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WO 2004/005286 A3

(51) International Patent Classification[7]: C07D 471/04, A61K 31/437, A61P 31/12 // (C07D 471/04, 235:00, 221:00)

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NEYTS, Johan** [BE/BE]; Heidebergstraat 278, B-3010 Kessel-Lo (BE). **PüRSTINGER, Gerhard** [AT/AT]; Roseggerstrasse 12, A-6020 Innsbruck (AT). **DE CLERCQ, Erik** [BE/BE]; Parklaan 9, B-3360 Lovenjoel (BE).

(74) Agents: **BIRD, William, E.** et al.; Bird Goën & Co, Klein Dalenstraat 42A, B-3020 Winksele (BE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

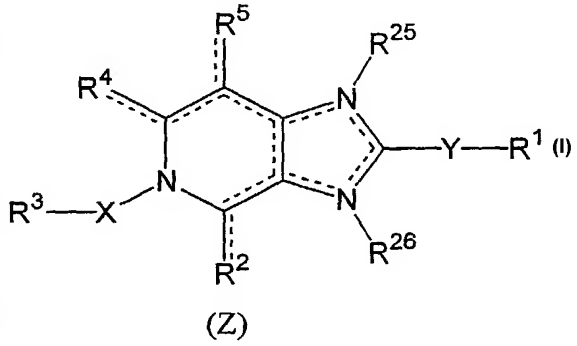
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 18 March 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/005286 A3

(54) Title: VIRAL INHIBITORS



(Z)

(57) Abstract: The present invention relates to a pharmaceutical composition for the treatment or prevention of viral infections comprising as an active principle at least one imidazo[4,5-c]pyridine derivative having the general formula (Z): (formula). The invention also relates to processes for the preparation of compounds according to the invention having above mentioned general formula and their use as a medicine or to treat or prevent viral infections.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/BE 03/00117

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P31/12 //(C07D471/04,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 158 440 A (ERBA FARMITALIA) 13 November 1985 (1985-11-13) page 4, line 3 -page 7; claims 1,9 ---	1
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YUTILOV, YU. M. ET AL: "Synthesis and antiviral activity of spinaceamine" retrieved from STN Database accession no. 110:165603 XP002265211 abstract & KHIMIKO-FARMATSEVTICHESKII ZHURNAL, vol. 23, no. 1, 1989, pages 56-9, --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2003	05/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/BE 03/00117

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HORVATH, A. ET AL.: "Preparation of sunstituted nitrogen-containing heterocyclic compounds" retrieved from STN Database accession no. 132:222537 XP002265212 RN=261379-92-4 & HU 78 019 A (HORVATH) 28 May 1999 (1999-05-28) ---	7
X	WO 99 27929 A (MERCK) 10 June 1999 (1999-06-10) example 4 (6) ---	7
X	WO 96 11192 A (SEARLE) 18 April 1996 (1996-04-18) page 207, example 358c ---	7
X	WO 96 12703 A (SEARLE) 2 May 1996 (1996-05-02) examples 11,18 ---	7
X	US 5 302 601 A (KHANNAL ISH K ET AL) 12 April 1994 (1994-04-12) examples ---	7
X	EP 0 344 414 A (SEARLE & CO) 6 December 1989 (1989-12-06) examples ---	7
X	WO 95 16687 A (ABBOTT LAB) 22 June 1995 (1995-06-22) examples ---	7
P,X	HISASHI AKAMATSU ET AL.: "New efficient route for solid-phase synthesis of benzimidazole derivatives" JOURNAL OF COMBINATORIAL CHEMISTRY., vol. 4, no. 5, 2002, pages 475-483, XP002265210 AMERICAN CHEMICAL SOCIETY, WASHINGTON., US ISSN: 1520-4766 pages 479, 480, compounds 15,16(21), 16(22) -----	7

INTERNATIONAL SEARCH REPORT

Inte onal application No.
PCT/BE 03/00117

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 7-14 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-14 (in part)

Present claims 7-14 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I described in page 19, line 15 - page 22, line 9.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/BE 03/00117

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna Application No
PCT/BE 03/00117

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 9516687 A1	22-06-1995

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/026606

A. CLASSIFICATION OF SUBJECT MATTER
C07D473/00 C07D471/04 C07D519/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS, EMBASE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15) examples, pages 46-52 and 87-89; page 4, lines 5-18 and pages 119-126 page 87 - page 89; examples	56-59,61
X	EP 1 132 381 A (CERMOL S.A) 12 September 2001 (2001-09-12) example 51	56-58,61
A	EP 1 162 196 A (JAPAN TOBACCO INC) 12 December 2001 (2001-12-12) abstract; claims	1-78

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2006	01/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Frelon, D

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/026606

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/20400 A (AXYS PHARMACEUTICALS, INC; HATAYE, JASON, M; RICE, KENNETH; SHELTON, E) 13 April 2000 (2000-04-13) page 1; claims	1-78
A	WO 95/02597 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 26 January 1995 (1995-01-26) abstract; claims	1-78
A	GB 2 158 440 A (FARMITALIA CARLO * ERBA S P A) 13 November 1985 (1985-11-13) abstract; claims	1-78
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YUTILOV, YU. M. ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" XP002367158 retrieved from STN Database accession no. 1989:165603 abstract & KHIMIKO-FARMATSEVTICHESKII ZHURNAL, vol. 23, no. 1, 1989, pages 56-59,	1-78
A	WO 01/95910 A (BRISTOL-MYERS SQUIBB COMPANY) 20 December 2001 (2001-12-20) abstract; claims	1-78
A	EP 1 386 923 A (SUMITOMO PHARMACEUTICALS COMPANY, LIMITED) 4 February 2004 (2004-02-04) abstract; claims	1-78
A,P	WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005 (2005-07-14) the whole document	1-78

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/026606

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 71-74 and 75-78 are directed to a method of treatment of the human/animal body and/or to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/026606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004005286 A	15-01-2004	AU 2003243846 A1	23-01-2004
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/026606

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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WO 2005063744 A	14-07-2005	NONE		

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 111.23F	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/043112	International filing date *(day/month/year)* 21.12.2004	Priority date *(day/month/year)* 22.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07D471/04 A61K31/437		
Applicant K.U. LEUVEN RESEARCH & DEVELOPMENT		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 20 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.10.2005	25.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Deutsch, W Telephone No. +49 89 2399-8281

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043112

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 4-243	as originally filed
3	filed with telefax on 05.12.2005

Claims, Numbers

1-69	filed with telefax on 05.12.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-69
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-69
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III

For the assessment of the present claims 64-69 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 64-69 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V and VI

Reference is made to the following documents:

D1: EP-A-1 132 381 (CERMOL S.A) 12 September 2001 (2001-09-12)
D2: US-A-5 302 601 (KHANNAL ET AL) 12 April 1994 (1994-04-12)
D3: US-A-4 990 518 (KHANNA ET AL) 5 February 1991 (1991-02-05)
D4: WO 96/12703 A (G.D. SEARLE & CO; KHANNA, ISH, KUMAR; STEALEY, MICHAEL, ALLAN; WEIER,) 2 May 1996 (1996-05-02)
D5: US-A-5 486 525 (SUMMERS, JR. ET AL) 23 January 1996 (1996-01-23)
D6: EP-A-0 076 530 (JANSSEN PHARMACEUTICA N.V) 13 April 1983 (1983-04-13)
D7: US-A-5 585 492 (CHANDRAKUMAR ET AL) 17 December 1996 (1996-12-17)
D8: US-A-5 137 896 (VAN DAELE ET AL) 11 August 1992 (1992-08-11)
D9: WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15)

D10: EP-A-0 417 745 (G.D. SEARLE & CO) 20 March 1991 (1991-03-20)

D11: WO 99/27929 A (MERCK & CO., INC; HALCZENKO, WASYL; STUMP, CRAIG, A) 10 June 1999 (1999-06-10)

D12: US-A-5 227 384 (KHANNA ET AL) 13 July 1993 (1993-07-13)

D13: US-A-5 446 032 (WHITTAKER ET AL) 29 August 1995 (1995-08-29)

D14: EP-A-0 344 414 (G.D. SEARLE & CO) 6 December 1989 (1989-12-06)

D15: US-A-5 011 832 (DININNO ET AL) 30 April 1991 (1991-04-30)

D16: GB-A-2 158 440 (FARMITALIA CARLO ERBA S P A) 13 November 1985 (1985-11-13)

D17: RYUICHI ET AL:: "Synthesis and Evaluation of Novel Nonpeptide Angiotensin II Receptor Antagonists: Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent" CHEM. PHARM. BULL, vol. 43, no. 3, 1995, pages 450-460, XP001206481

D18: THOMAS D. PENNING ET AL.: "Synthesis of Imidazopyridines as Potent Inhibitors of Leukotriene A4 Hydrolase" BIOORGANIC AND MEDICINIAL CHEMISTRY LETTERS, vol. 13, 2003, pages 1137-1139, XP002333169

D19: YUTILOV YU M ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" 1989, CAPLUS , XP002265211

D20: G.B. BERLIN, "Ionisation Constants of Heterocyclic Subsatnces, Part VIII, 1,3,5 Triazindenes, Physical, Journal of the Chemical Society[SEction B]: Physical Organic, vol.4 , 1966, pages 285-291

D21: RYUCHI KIYAMA"Synthesis and Evaluation of Novel NonpeptideAngiotensin II Receptor Antagonists": Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent, Chem. Pharm. Bull. 43(3), pages 450-460.

D22: GERHARD CLEVE ET AL., Derivate des Imidazo[4,5-b]- und Imidazo[4,5-c]pyridins., Liebigs Ann. Chem., 747,1971, pages 158-171

D20-D22 were cited in the internationational search report, but are mentioned in the description of the present application.

D9 has a publication date, which is prior to the filing date of the present application. It may be noted that D9 has entered the European phase of examination.

The present claims do not appear to be entitled to the earlier priority date of 22.12.2003, such that D9 is relevant both for the examination of novelty and inventive step.

Novelty

Novelty destroying subject matter

Example 51 of D1 is novelty destroying to the present claim 1.and a number of further claims. (The subject matter of the claims differs from further examples in D1 from through the fact that R^3 does not include saturated heterocycles).

5-[(4-fluorophenyl)methyl]-N-methyl-5H [4,5-c]pyridine-2-amine disclosed on page 75, lines 26-27 of D6 and column 43, lines 38 and 39 of D8 is still novelty destroying to the present claim 1 and a number of further claims.

The subject matter of the present claims overlaps with that of D9. This overlap is considered to be novelty destroying to the present claims.

D9 also contains numerous examples in table 8, which are novelty destroying for the present claims e.g. entry 2,3, 5, 12, ,24, 26 etc. The number of compounds, which are novelty destroying to the present claims which are novelty destroying will depend on the final interpretation of the term "aryl" and "aromatic heterocycle"(see section VIII). Thus e.g.entry 23 of D9 could be novelty destroying for a number of claims.

Differences with subject matter of cited documents

The compounds of the present claims differ from the compounds of D2- D4, D7, D10-D15, D17, D21 through the proviso introduced into claim 1, that Y-R^1 is not hydrogen or alkyl or in the case of claim 56 that Y-R^1 does not include alkyl or hydrogen.

The compounds of the present claims are considered to be a novel selection from those generally disclosed in D5. The compounds of the present claims either differ from those specifically disclosed in D5 through the proviso that Y-R^1 is not alkyl or through the R^3-X group in claim 56.

The imidazopyridine derivatives of the present claims differ from those of D16 through the number of double bonds. In claim 1 of the present claims it is indicated that the dotted lines represent at least 3, whereas in the compounds of D16, there is only 1 double bond in the tetrahydroimidazopyridine structure.

The compounds of the present claim 1 differ from 1,4,6,7-tetrahydro-1-methyl-2-(methylthio)-alpha-phenyl-5H-imidazo[4,5-c]pyridine-5-ethanol disclosed in D19 through the the number of double bonds in the bicyclic structure, through the proviso that when when one of R^{25} or R^{26} is present then either R^2 or R^4 is selected from (=O), ((=S) and (=NR^7), and the OH group.

The compounds of the present claim 1 differs from that of 5methyl-2-methylthiotriazaindene disclosed in D20 through the proviso that when when one of R^{25} or R^{26} is present then either R^2 or R^4 is selected from (=O), ((=S) and (=NR^7).

It has been assumed that the term "aryl" in claim 1 does not include substituted aryl. In this case compounds 9a and 9b of D22 (page 747) are not novelty destroying to the present claim 1, 48 and 56 (see however section VIII). However, final interpretation will depend on the course of the examination, at the regional stage.

Inventive Step

The closest prior art is considered to be D9, in view of the novelty destroying subject matter that this contains and in that it relates to compounds having antiviral activity.

In view of the disclosures of D9, the skilled person would readily have arrived at the claimed subject matter.

The problem underlying the invention is considered to be the provision of further imidazopyrimidine compounds having a surprising activity compared to the closest prior art.

In the absence of any evidence for such a surprising effect an inventive step cannot be acknowledged.

Furthermore an inventive step cannot however be acknowledged for the present claims for the following reasons:

Reasonable alternatives to the tested examples are allowable. The claims however include modifications of substituents which would not reasonably be expected to solve the problem underlying the invention having regard for common knowledge and biological structure-activity relationships.

The question as to what extent the structure of a chemical compound can be modified without causing major changes in its biological activity is considered to be equally relevant in respect of the question as to whether or not it is credible that all members of a certain group of chemical compounds solve a particular problem.

In the present case the structural differences on passing from the examples to compounds falling in the claims are far greater than the structural differences between compounds falling under the claims and compounds according to the prior art D16 and D19.

For example In the present case -Y-R^1 is limited to halophenyl compounds, whilst Y-R^1 includes variations, which are structurally completely different to this.

VIII

a)The description has not been amended to the new set of claims, leading to an inconsistency between the claims. The present claims are therefore not supported by the description as required by Article 6 EPC.

In this respect the following is to be noted.

-The description refers to the exclusion of various compounds as required on page 28, last line to page 31, line 3. The different scope of exclusion and the fact that they need not be excluded in the description leads to an inconsistency with the claims,

The Applicant has indicated that these disclosures could be removed from the description in due course, if these are not required as a basis for a proviso to distinguish the claim from the prior art.

-There is an inconsistency between the claims and description with respect to the term "aryl", such that the meaning of the claims is not clear from the wording alone.

Thus according to the claims R^3 may be aryl which may be substituted by M-Q.

"Aryl" would normally be understood according to the IUPAC rules as only containing carbon and hydrogen. Since M-Q cannot be e.g. fluorine or CF_3 and these substituents are found on the phenyl group in e.g. example 19 and 20, there is an implication in the light of the description that aryl is intended to encompass "optionally substituted" aryl.
This appears to be supported from the compounds which it is intended to exclude from the invention (see e.g. page 26, lines 30-34).

Similar arguments apply to "aromatic heterocycle".

b)The reasons for the provisos in the claims are only partially explained by the cited prior art and it will become necessary to consider more closely the reasons for the provisos in the present claims.

For example, the proviso may be directed to the exclusion of known prior art compounds which do possess the desired activities.

If in this case, if the said prior art was published before the priority date of the application, it may be necessary to take the prior art into consideration for the assessment of inventive step.

Similarly the reason for the possible exclusion (a) on page 26 and page 29, lines 23 page 29, line34and page 33, line 35

Furthermore it may be necessary to consider why there are differences in the scope of proviso in claims 1 and 2 with respect to the substituent R^3 and is absent in claim 3.

b) The expressions "an amino acid residue" in the claims is considered to be unclear, since the expression gives no indication which part of the molecule of said compounds is intended as substituent. For example the amino acid residue could be such diverse groups as a COOH group, a CH_3 group a HO-benzyl group or HO-benzyl-CH_2-CH(COOH)-NH-. Furthermore it is unclear whether amino acid residue encompasses only the common natural amino acids or whether it is also intended to cover synthetic amino acids or less common amino acids.

If not all of the diverse possibilities are intended e.g. methyl, it is unclear where the bordelines for the definition lie.

The meaning of the terms of a claims should be as far as possible be clear from the wording alone. The expression "an amino acid residue as used in the claims relies on the description for its interpretation".

c) Having regard for claims 1, 2, 3, 48, 56 it appears that these are independent claims. It is however considered that it would be appropriate to cover these by a single independent claim.

d) a lack of clarity arises with certain R^6 substituents, which are unstable. Thus for example OH substituted by -O-alkenylC(=O)OR^{18}.

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 111.28PF	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/046477	International filing date *(day/month/year)* 21.12.2005	Priority date *(day/month/year)* 21.12.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D471/04		
Applicant GILEAD SCIENCES, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2006-10-20	16.03.2007
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stroeter, Thomas Telephone No. +49 89 2399-8088

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-16 as originally filed

   Claims, Numbers

   1-5 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3,4

because:

☒ the said international application, or the said claims Nos. 3,4 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-5 YES
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5 YES
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1,2,5 YES

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 3 and 4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The present application is directed to a compound which is useful in the treatment of viral infections including hepatitis C virus.

2 Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004

D2: WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005

Concerning document D2 please see item VI.

3 The presently claimed compound differs from the structurally closest prior art compounds revealed in D1 which are also antiviral compounds through the phenyloxazolyl group instead of a phenyl or pyridyl group. This structural modification starting from the compounds of D1 in order to solve the problem of providing an alternative antiviral compound useful in the treatment of HCV is not obvious and thus, compound claim 1 and consequently further claims 2-5 appear to be novel (Article 33(2) PCT) and inventive (Article 33(3) PCT).

However, it is remarked that the findings on inventive step are made on condition that experimental data can be provided at a later stage to support that the claimed compound indeed shows the alleged pharmacological effect and as such solves the

problem posed.

4 The subject-matter of the present claims 1, 2 and 5 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present claims 3 and 4 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

The International Search Report mentions P-document D2 which does not form part of the state of the art according to Rule 64.1(b) PCT and thus was not discussed under item V of this report. Since the present priority has been validly claimed, D2 disclosing the compound of example 6 and related subject-matter is not novelty-destroying for present claim 1-5.

Re Item VII
Certain defects in the international application

When entering the regional phase at the EPO, the expression "incorporated by reference" is to be deleted wherever it may appear in the present description.

Corrected V

PCT

WIPO PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 626.PF	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/026606	International filing date *(day/month/year)* 26.07.2005	Priority date *(day/month/year)* 27.07.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D473/00 C07D471/04 C07D519/00 A61K31/52		
Applicant GILEAD SCIENCES, INC. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 19 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 43 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.05.2006	20.02.2007
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Frelon, Didier Telephone No. +49 30 25901-312

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/026606

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-8, 11, 14-51, 54-56, 61, 68, 70-73, 76-83, 87-110, 112, 114-124	as originally filed
9, 10, 12, 13, 52, 53, 57-60, 62-67, 69, 74, 75, 84, 85, 111, 113	filed with telefax on 31.05.2006
86	filed with telefax on 13.11.2006

Claims, Pages

125-127, 129-135, 137-140	filed with telefax on 31.05.2006
128, 136	filed with telefax on 13.11.2006

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 62-69

because:

☒ the said international application, or the said claims Nos. 62-69 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-69
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-69
Industrial applicability (IA)	Yes:	Claims	1-61
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

1. Amendments

Claims 1 to 55 on file repeat originally filed claims 1 to 55. Claims 56 to 69 on file repeat originally filed claims 64 to 68 and 70 to 78, respectively.

In reply to the WO-ISA of 01.03.2006, the Applicant has brought amendments within his replies received on 31.05.2006 and 13.11.2006 which consist essentially of the deletion of originally filed claims 56 to 63 and 69 (which was redundant with original claim 66). The remaining claims have been consecutively renumbered 1-69. The disputable term "isomers" has been deleted from claims 1, page 128 and 48, page 136.

In the description, formal amendments have been done:
- on pages 9, 10, 12, 13, 52, 59, 60, 62-67, 69, 74, 84 and 86, the expression "and the like" has been deleted.
- on pages 58, 59, 85, 111 and 113, "etc" has been similarly deleted. Note that most of such deletions have no effect when the affected sentence still contains a verb like "includes" or other enlarging expression like "but are not limited to" or "and so on".
- on page 75, the broadening introduction to the examples has been deleted.
- on said amended pages 53 and 57, the amendments are not clearly apparent.

It appears that the amendments have only excluded the subject-matter of original claims 56 to 63 which was considered to be non unitary. *The limitations of the searched scope have not been taken into account. The pending objections remain valid against the amended application.*

2. Scope limitation

The present claims 1-55, 61-69 relate to an extremely large number of possible compounds (claims 56-60 are directed to specific examples of the illustrations). In addition, it is noted that unspecific and/or open expressions like *aryl, heterocycle, aminoacid residue, ring, linking group, isomers* add to the lack of clarity and conciseness of the claims (see points 3.3.1ff, below). It is not said that a term like alkyl is not clear per se, but that the

combination of the numerous unspecific terms results in unclearly claimed subject-matters. The argument that recitation of subgenera may increase the complexity of the claims and reduce the conciseness cannot be accepted. Conciseness is not necessarily synonym of shorthand, abridgment, etc, particularly when the terms used for their theoretical conciseness do not cover meanings which are usually understood by the skilled person. Relevant repetitions may be necessary to set clarity. On the contrary, excessive "conciseness" is source of unclarity due to inconsistencies between the claims and the description where certain embodiments are said to be excluded (pages 17-20), partly referring to prior art documents (possibly said "incorporated by reference") or their family members. But the claims do not reflect this. Since it is the claims which define the matter for which protection is sought, if these exclusions correspond to a relevant prior art which is not come to the knowledge of the examining division, the claims could be considered to be anticipated by these compounds. Furthermore, if the said prior art was published before the priority date of the application, it may be necessary to contemplate this prior art for the assessment of inventive step.

The "formula" (A) in claim 1 or on page 3 is understood to be intended to cover a scope as large as possible but, as drafted, it goes against the requirements of the PCT for clarity and conciseness. A said Markush formulation can be a very useful and efficient way to claim a group of compounds, but it is not exempt to comply with clarity and conciseness requirements (Art. 5 and 6 PCT). It is understood that the Applicant expects that the full scope of the claimed subject-matter be searched, but this must be feasible and, for this purpose, the said scope must be clearly and concisely described. That is also why embodiments and illustrations by examples are useful to supply unspecific deficiencies. For instance, due to the dotted lines which should represent optional double bonds, the rests R^2, R^4 and R^5 are ill-defined since their definitions do comprise only monovalent groups which thus cannot link the imidazopyrimidine core twice. It would have been probably preferable to draw several figures, provided they comply with the unity requirements (Art. 3(4)(iii) PCT). A consequence is the impossiblity to determine the extent of the search because it cannot cover meaningfully an ill-defined claimed scope.

The first -relatively- clear and concise representation of a group of compounds could only be found with figure (A1), description page 28 [given that, since U is N, the rest R^5 is not optionally but *necessarily* absent - note that, if the nitrogen of the 4-position should be

quaternized, the definition of the claimed compounds would lack further clarity and conciseness because the definition of any necessary counterion would be absent] and with the prepared examples which are concrete forms of the invention: the search can only be made for a clear and concise subject-matter which is the first clear and concise subject-matter actually given by the Applicant in the specification. It was therefore certainly not arbitratry to focus the search as done since it followed the first indications made clear and concise by the Applicant.

Support and disclosure in the sense of Art. 6 and 5 PCT is to be found for only a very small proportion of the compounds claimed (see prepared examples 1-6 of pages 117-121) wherein (designation of figure (A1)):
- R^2, R^4 are H (R^5, R^{25} and R^{26} -designation of (A)- are necessarily absent due to the ring nitrogen valency),
- X represents CH_2,
- Y is a bond,
- R^1 is a (fluoro substituted) phenyl and
- R^3 represents a (trifluoromethyl or trifluoromethoxy substituted) phenyl or an isoxazole substituted by a (propoxy or chloro substituted) phenyl.

It will be also apparent to the skilled person that figure (A1), page 38, represents quite a large generalization of (a reasonable "penumbra around") the illustrations (see also points 3.3.1ff, below). The limitation of the search was consequently not arbitrary but guided by the subject-matter of the description which is consistent considering: YR^1 and R^3 = (hetero)ring and X = Alk, AlkO, AlkS or AlkN.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims (PCT Guidelines 9.19 and 9.23).

The search was necessarily restricted to those claimed compounds which appear to be supported and to a generalisation of their structural formulae, as described in formulae (A1) (said "fourth aspect" of the invention, page 27).

Re Item II

Due the presence of an intermediate document, the claimed priority date of 27.07.2004 had to be checked. It results that the priority is NOT valid when:

- R^1 is selected from C_1-C_{10} alkoxy, C_1-C_{10} thioalkyl, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino and C_4-C_{10} cycloalkynyl
- R^2 and R^4 are independently selected from haloalkyloxy (except OCF_3) and heterocycle (except 5- ot 6-membered heterocyclic),
- R^3 is selected from cycloalkyl (except C_3-C_{10} cycloalkyl), cycloalkenyl (except C_4-C_{10} cycloalkenyl), cycloalkynyl and heterocycle (except 5- ot 6-membered heterocyclic),
- R^5 is selected from haloalkyloxy (except OCF_3) and heterocycle (except 5- ot 6-membered heterocyclic),
- R^6 is selected from C_1-C_{18} alkylsulfoxide, C_1-C_{18} alkylsulfone, C_1-C_{18} haloalkyl, C_2-C_{18} haloalkenyl, C_2-C_{18} haloalkynyl, C_1-C_{18} haloalkoxy, C_1-C_{18} haloalkylthio, cyanoalkyl, -$C(O)OR^{18}$, arylsulfoxide, arylsulfone, arylsulfonamide and heterocycle (except 5- ot 6-membered heterocyclic),
- R^7 and R^8 are independently selected from heterocycle (except 5- ot 6-membered heterocyclic) and, when taken together with the nitrogen to which they are attached, they form a heterocycle (except 5- ot 6-membered heterocyclic),
- R^9 and R^{18} are independently selected from $CH_2CH(=O)R^{9a}$ and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl,
- R^{10} and R^{11} are independently selected from heterocycle (except 5- ot 6-membered heterocyclic) and an amino acid residue (when not linked through a carboxyl group thereof),
- R^{12} is an amino acid residue (when not linked through an amino group thereof),
- R^{15} and R^{16} are independently selected from arylalkyl (unsubstituted or substituted with $C(O)OR^{18}$) and an amino acid residue (when not linked through a carboxyl group thereof),
- R^{17} is selected from

(a) C_1-C_{18} alkylsuloxide, C_1-C_{18} alkylsulfone, C_1-C_{18} halogenated alkyl, C_2-C_{18} halogenated alkenyl, C_2-C_{18} halogenated alkynyl, C_1-C_{18} halogenated alkoxy, C_1-C_{18} halogenated alkylthio, CO_2R^{18}, haloalkyloxy (except OCF_3), arylsulfoxide, arylsulfone, arylsulfonamide, heterocycle (except 5- ot 6-membered heterocyclic) and

(b) M-Q- wherein M is a ring optionally substituted with a or more R^{19}, and Q is a bond or a linking group connecting M to R^3 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with one or more R^{19}.

- R^{19} is selected from
(c) sulfone, sulfonamide and sulfoxide,
(d) C_1-C_{18}, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl substituted by C_3-C_{10} cycloalkyl, C_4-C_{10} cycloalkenyl, C_4-C_{10} cycloalkynyl, aryl or heterocycle,
(e) C_1-C_{18}, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl wherein 1 or more methylene are replaced by 1 or more O (except C_1-$_{18}$ alkoxy), S (except C_1-$_{18}$ alkylthio), NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$,
(f) further substitutions of (c) and (e) by C_3-C_{10} cycloalkyl, C_4-C_{10} cycloalkenyl, C_4-C_{10} cycloalkynyl, aryl or heterocycle,
(g) heterocycle and C_3-C_{10} cycloalkyl, C_4-C_{10} cycloalkenyl, C_4-C_{10} cycloalkynyl, aryl or heterocycle further substituted with C_{1-6} alkyl, $C(O)OR^{12}$, =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$,
(h) $C(O)R^{18}$ and $C(S)R^{18}$ [wherein R^{18} is $NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group thereof, $CH_2CH(=O)R^{9a}$ and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl], $C(O)OR^{18}$ and $OC(O)R^{18}$ [with the full definition of R^{18}] and $C(O)N(R^{12})_2$ [except when one R^{12} is H and the other is C_{1-6} alkyl],
(i) to (k) further substitutions defined in the application on file
- R^{20} and R^{21} are independently heterocycle (except 5- ot 6-membered heterocyclic)
- R^{25} and R^{26} are independently heterocycle (except 5- ot 6-membered heterocyclic and pyridyl optionally substituted with 1 to 4 C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy and OH),
- R^{27} is arylC_{2-18} alkyl.

None of the specific compounds prepared in the application is disclosed within the priority document. Where the priority date is not valid, the intermediate document D10 is therefore relevant for the purposes of Rules 33.1c, 64.3 and 70.10 PCT (see section VI, certain documents), *i.e.* relevant in order to assess whether the claims satisfy the criteria set forth in Art. 33(1) PCT.

D10 may also be a relevant prior art with regard to inventive step (compounds of D10 are essentially different by the presence of a carbon atom in place of U) in a regional or national phase.

Re Item III

Claims 62-69 are directed to methods for treatment of the human or animal body by surgery or therapy and/or to diagnostic methods practised on the human or animal body. They relate to subject-matter considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of these claims on the question whether their subject-matter is industrially applicable, no unified criteria exist in the PCT Contracting States. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT). The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treament and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. Cited documents

D1: WO 2004/005286
D2: EP 1 132 381
D3: EP 1 162 196
D4: WO 00/20400
D5: WO 95/02597
D6: GB 2 158 440

D7: DATABASE CA [Online]; YUTILOV, YU. M. ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" Database accession no. 1989:165603

D8: WO 01/95910

D9: EP 1 386 923

D10: WO 2005/063744 (intermediate document)

2. Novelty

With the amendments (claims deletion) brought in answer to the previous written opinion, the objection of non unity has been overcome.

In the frame of the limited searched scope (see item I), compounds of formula (A) [*i.e.* (A1)] appear to be novel. These novel compounds, *i.e.* imidazo[4,5-d]pyrimidine derivatives (*i.e.* wherein U = N), are characterized by their substitution pattern such that the groups Y-R^1 and R^3 represent a ring (Y is a single bond).

3. Inventive step

3.1 The problem underlying the present application is to provide antiviral compounds. Compounds of D1 can be considered as the closest prior art in view of the part of the subject-matter which is entitled to the priority date. Compounds of D10 can be considered to be the closest prior art for the part of the subject-matter which is not entitled to the priority date.

3.2 The essential difference of the claimed subject-matter and the prior art is in both cases essentially to be seen in the replacement of a ring carbon atom by a nitrogen in place of U, *i.e.* in the condensed system wherein the ring carbon atom of the 7-position of the imidazopyridine is replaced by a nitrogen atom to form the present imidazopyrimidine. Such an exchange belongs to the general knowledge of bioisosterism of C and N as ring members. Document D3 which also belongs to the field of antiviral compounds illustrates the usual knowledge in drug design studies that carbon atom and nitrogen atom are commonly considered to be exchangeable unless a well known prejudice in the particular

domain of viral inhibitors would restrain the skilled person from proceeding with the C/N replacement. Similarly, X_8 of formula II in D4 and the ring members A, B, D and E in D8 illustrate this common knowledge. Even D2 which was cited against the novelty of the deleted claims confirms this very general knowledge with the ring members V and W which represent C or N. The Applicant did not bring the evidence that the present invention overcomes a known prejudice. The skilled person facing the problem mentioned above comes therefore directly to the solution of the present application.

The specification only describes assays and is silent about their concrete results. The qualification of the activity as excellent or of the toxicity as low lacks to point any reference which could give the significance of these qualities in order to substantiate the presence of an inventive step.

In order to show that the novel compounds are inventive, it must be clearly apparent that the differentiating feature is responsible for an unexpected effect. If this demonstration should be made by means of comparative tests, the compounds to be compare should be chosen such that they only differ by the diffentiating feature.

3.3 The Applicant's attention is drawn to the fact that, despite the limitations which were mandatory for the search (see item I), the claims do not fully satisfy PCT requirements. Particularly, the protection which is sought should comply with a reasonable breadth for the claimed scope.

3.3.1 It is realized that the Applicant is entitled to claim all **obvious** modifications of what was concretely described and that alternative variations have to be supported by the description, *i.e.* a certain number of examples.

Open and non limitative (generalizing) expressions or terms like "*aryl, heterocycle, ring, linking group, aminoacid residue, etc*", derivatives thereof extend (irrealistically) the scope of the claims beyond what has actually been verified in the worked examples on file. For instance, the amino acid residue could be extremely different groups. Furthermore it is unclear whether an amino acid residue encompasses only the residue of a natural amino acid or whether it is also intended to cover a synthetic amino acid residue.

Undefined terms render the claims **obscure in scope** and do not allow to correctly and specifically circumscribe a scope where the invention applies and for which protection can actually be granted.

There should be no confusion between the clarity of certain terms (*i.e.* a straightforward comprehension which is not disputed) and the scope covered by these terms (*i.e.* an unlimited and therefore disputable extent) with the clarity and conciseness of the claims (Art. 6 PCT). Art. 6 PCT states unambiguously that the claims shall define the matter for which protection is sought. It is not said that they are defined "by reference to the description" but that they must be supported by the description. If a term in a claim actually includes a restriction, like here concerning the positional isomers, which is only mentioned in the specification, and if this restriction is not clear (even implicitly) from the text of the claim, the claim cannot be considered as fulfilling the requirements of clarity and conciseness.

The question is whether or not a technical effect is to be achieved by all the embodiments covered by the claims when this technical effect turns out to be the sole reason for the alleged inventiveness of these processes. A consequence is that broad expressions are objectionable under Art. 33(3) PCT. This is not only a question of terminology about the support for a scope and thus of "recasting" basis issues; the purpose is clearly a technical question whether the inventivity is credibly present over the whole claimed scope. Formal matters (clarity, support, etc) and obviousness are not "intermixed", although it cannot be denied that the corresponding objections are necessarily linked and cannot be artificially separated.

A legal principle is that the extent of a patent monopoly is justified by the technical contribution to the art. This principle which is applied in relation to the extent of the protection that is justified by reference to Art. 5 and 6 PCT also governs the decision which is required to be made under Art. 33(3) PCT, for everything falling within a valid claim has to be inventive. Judgement of inventive step depends on whether the specific technical purpose (a surprising or unexpected correlation between a structure and an activity) can be credibly achieved over the whole range claimed. A second legal principle is that any one who alleges a fact has the onus of proving this allegation by appropriate evidence. The fact that test results show that ***some*** of the claimed compounds are indeed active

cannot be regarded as sufficient evidence to lead to the inference that substantially ***all*** the claimed compounds possess this activity. The burden of proof that all the compounds claimed possess the alleged activity rests only upon the shoulders of the person alleging it.

3.3.2 The (given) examples (and particularly the tested ones) represent a relatively narrow illustration of the claimed scope (they have been already taken as a basis for the limitation of the search scope presently examined). It can be therefore questioned whether the regularly occuring groups in the examples form a necessary and essential characterisitic of the invention which should not be allowed to vary out of the ***reasonable*** extent of the usual equivalents and (bio)isosters of these variants, (especially keeping in mind that the difference with the prior art is relatively small, the effect (to be unexpected for an inventive step recognition) of which can be hindered by other unpredicted effects of larger structural variations of other variant groups that a skilled person cannot consider as obvious equivalents). In the present case the structural differences on passing from examples to compounds falling in the claims are far greater than the structural differences between compounds falling under the claims and compounds according to the prior art. Without any evidence of the contrary, the claimed scope do not represent a reasonable generalization of the very invention as shown by the examples.

Generalisations of concrete examples appear to be acceptable if they are not contradictory to the basis of qualitative or quantitative structure-activity-relationships (SAR) which says that for compounds with a certain chemical basic structure the known biological activity can *prima facie* be expected to be retained when making small structural modifications. These principles are well known to skilled persons in pharmacology and drug design and, if such principle would no longer apply at all, no generic formula in claims would be allowable at all for a pharmaceutical patent which then logically would have to be restricted to the concretely tested example(s).
It appears to be contradictory, on one hand to argue that, thanks to a very small structural modification on a position in a molecule, the known biological activity is surprisingly maintained or improved and, on the other hand, to claim a large number of structurally very different families of substituents through the above disputed terms (and their combinations) at various positions of the molecule under consideration.

Reasonable predictions of relations between chemical structures and biological activities

are in principle possible, but **there is a limit** beyond which no such prediction can be validly made. It is therefore necessary to fix limits to unspecific terms.

3.3.3 Open and too broad formulations may also lead to unacceptable **speculations** from the skilled people as to the very invention and its future aspects; it may even suggest that the claimed scope lacks any inventive merit and is not properly covered by the description and, particularly, the examples. Furthermore this would deprive any third party from a legitimate protection for a genuine invention in relation with an object which was neither described nor even foreseen but would have only been a hypothesis in the frame of the present invention.

When only some and not substantially all claimed compounds exhibit a particular technical effect, the conclusion has to be that the invention as broadly defined in the independent claim was not a solution to the technical problem of achieving the given technical effect (with the consequence that the alleged technical effect of some of the claimed compounds is to be disregarded when determining the objective problem underlying the invention and thus when assessing inventive step). In other words, a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the selected compounds. A general formulation, made up of many variables or groups defined by unlimited and/or vagues terms or non limitative expressions (including unspecific points of attachement), constitutes an excessive generalization encompassing forms which go far beyond what the skilled person, also taking into account physico-chemical and biological considerations, can regard as including obvious modifications, equivalents and/or (bio)isosterical values of substituents/of the examples given in the description.

There is indeed a great variety of structural possibilities which are claimed (and not yet explored by the Applicant), the *effect of which cannot be foreseen* having regard to the problem underlying the present application and, consequently, which are not solutions of the problem. Note that the Applicant's assertions as to the activity of the compounds is not questioned. They are believed to be active (point 3.2 above). The question is whether the claimed compounds develop any surprising effect which can serve as an objective basis to prove the presence of an inventive step.

3.3.4 The inventive step required by Art. 33(3) PCT can be acknowledged only for a well-defined scope embracing a specific domain thanks to a reasonable generalisation of the very invention, taking into account the extent of the illustration of the examples, the support of the specification, the closeness of the prior art, the reproducibility and the feasability of the invention. In other words, the protected scope should comprise only compounds, their variants and equivalents which solve the problem underlying the invention, (what is a prerequisite for the acknowledgement of an inventive step).

As chemical species can be precisely defined by the identity and the number of the atoms involved, it is necessary to specify the disputed expressions and terms by means of the incorporation of the definitions given in the specification.

Re Item VI

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2005063744	14.07.2055	21.12.2004	22.12.2003 02.01.2004 26.07.2004

Re Item VII

To meet the requirements of Rule 5.1(a) PCT, cited prior art documents should be identified in the description and the relevant background art disclosed therein should be briefly discussed. It is clear that, after amendments and clarifications, only relevant documents, *i.e.* closest prior art documents, are concerned.

Re Item VIII

1. Any expression or sentence which may also refer to an extent of protection beyond the actual invention is also objectionable (cf. "but are not limited to", "and so on"). The

insertion of such sentences and/or part of sentences would suggest that the subject-matter as presently disclosed does not cover properly the claimed scope. Any expression which can be interpreted as an unjustified extension of the claimed scope should be objected. The specification should be clear and sufficient by itself. A precautionary measure on the limits of the scope is therefore superfluous and even misleading as it finally prevents a proper definition of the invention and opens the way to speculations (of skilled persons) about the very inventive subject-matter. Consequently any element against clarity has to be deleted. In this sense, the expression "incorporated expressly herein by reference" is irrelevant and should be deleted. Note that, if the citations are "harmless" and do not affect the claimed scope, they are not necessary to a proper disclosure of the invention and there maintenance can be even misleading to the reader.

2. It is additionally noted that the terms and/or expressions such as "etc", "and the like" are unspecific. They cannot serve as a support for the invention and therefore should be deleted. Note that parts of the description which are obviously not related to the claimed subject-matter like definitions of groups which are not even mentioned in the claims should also be deleted.

The description refers to the exclusion of various compounds on page 20. The different scope of exclusion and the fact they need not be excluded in the description leads to an inconsistency with the claims.

3. References to methods of treatment or diagnostic methods as "embodiments" or as a further object or aspect of the invention should have been avoided since they are considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT. References to metabolites or isomers as further objects of the invention should have been avoided as well.

4. The reference to WO 00/204425 in the description is erroneous and should read WO 02/04425.

5. The reference to WO 2004/05286 (= D1) in claim 68 is considered to be irrelevant: (a) it refers to compounds which are not covered (as far as the given structure is clear) by the formula of the compounds (A1) of the searched invention which is the object of the present

Examination report, (b) the Applicant is reminded that whenever certain matter in a document is essential to satisfy the requirements of Art. 5 PCT, it should be expressly incorporated in the description because a patent specification should, regarding the essential features of the invention, be self-contained, *i.e.* capable of being understood without reference to any other document.

cyclopentyl, cycloheptyl, cyclooctyl, or a C_{7-10} polycyclic saturated hydrocarbon radical having from 7 to 10 carbon atoms such as, for instance, norbornyl, fenchyl, trimethyltricycloheptyl or adamantyl.

"Alkenyl" means a hydrocarbon moiety with at least one site of double bond unsaturation where the moiety may be acyclic, cyclic or a combination of acyclic and cyclic portions. The acyclic portion may contain 1 to 3 carbon atoms, and each cyclic portion may contain 3 to 6 carbon atoms. A site of double bond unsaturation may be in a acyclic portion, a cyclic portion. In the instance of a moiety having a combination of acyclic and cyclic portions, there may be a site of double bond unsaturation in each of the portions. Within this definition, the term "cycloalkenyl" refers to the double bond unsaturated hydrocarbon moieties that are cyclic. Examples the term "alkenyl" include, but are not limited to, ethylene or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), cyclopentenyl (-C_5H_7), 5-hexenyl (-$CH_2CH_2CH_2CH_2$CH=CH_2), 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, and 1-cyclohex-3-enyl. The double bond optionally is in the cis or trans configuration.

"Alkynyl" means a hydrocarbon moiety with a least one site of triple bond unsaturation where the moiety may be acyclic, cyclic or a combination of acyclic and cyclic portions. The acyclic portion may contain contain 1 to 3 carbon atoms, and each cyclic portion may contain 7 or more carbon atoms. Within this definition, the term "cycloalkynl" refers to triple bond unsaturated hydrocarbon moieties that are cyclic. Examples of the term "alkynyl" include, but are not limited to, -CCH, -CH_2CCH, -CH_2CC-cyclohexyl, or -CH_2-cycloheptynyl.

The suffix "-ene" used in connection with alkyl, alkenyl and alkynyl groups refers to such groups with at least 2 sites of substitution. Such polyvalent hydrocarbon radicals include, but are not limited to, methylene (-CH_2-) 1,2-ethylene (-CH_2CH_2-), 1,3-propylene (-$CH_2CH_2CH_2$-), 1,4-butylene (-$CH_2CH_2CH_2CH_2$-), 1,2-ethylene (-CH=CH-), -CC-, propargyl (-CH_2CC-), and 4-pentynyl (-$CH_2CH_2CH_2$CCH-). Optionally, alkylene, alkenylene and alkynylene are substituted with O, S or N, generally meaning that O, S or N replace a carbon

atom and the valence appropriate number of carbon substituents (generally 1 or 2H). N in this case is generally R^{11}.

"Aryl" means an aromatic hydrocarbon containing 1 or more rings, generally 1, 2 or 3, with 4 to 6 carbon atoms in each, ordinarily 5 or 6 carbon atoms.

"Arylalkyl," "arylalkenyl" and "arylalkynyl" means an alkyl, alkenyl or alkynyl radical, respectively, in which one of the hydrogen atoms, typically a terminal or sp3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl.

As noted, carbocycles optionally are found as single rings or multiple ring systems. Ordinarily the hydrocarbons of the compounds of the formulas of this invention are single rings. Monocyclic carbocycles generally have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system.

If the number of carbon atoms is unspecified for a hydrocarbon, typically the number of carbon atoms will range from 1 to 18, except that the number of carbons typically will range from 2 to 18 for unsaturated hydrocarbons and from 6 to 10 for aryl.

"Heterocycle" or "heterocycle" means any 4, 5, 6, 7, 8 or 9 membered single or fused ring system containing one or more heteroatoms selected from the group consisting of O, N or S. Heterocycles optionally are entirely aromatic, entirely saturated, or contain 1 or more intra-ring sites of unsaturation, typically double bonds. Multiple heterocyclic rings (one or more of which contains a heteroatom) are bridged or spiro. Generally, the heterocyclic rings will be aromatic, and usually they are single rings. Examples of heterocycles include oxazacyloalkyl, morpholinyl, dioxacycloalkyl, thiacycloalkenyl, pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, furanyl, thienyl,

2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

Nitrogen containing heterocycles are bonded at nitrogen or a carbon, typically a carbon atom. These include, for example, position 1 of aziridine, 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, 1-piperidinyl, 2-pyrroline, 3-pyrroline, 2-imidazoline, 3-imidazoline, 9-carbazole, 4-morpholine, 9-alpha or ß-carboline, 2-isoindole, 2-pyrazoline and 3-pyrazoline, and by analogy, azetidine, pyrrole, pyrrolidine piperidine, piperazine, indole, pyrazoline, indoline, imidazole, imidazolidine, 1H-indazole and isoindoline. These and other N-containing heterocycles are well-known to those skilled in the art, and their linkage sites are a matter of discretion.

Sulfur containing heterocycles are bonded through carbon or sulfur. They include oxidized states such as -S(=O)(=O). In general, they are linked in the compounds of the formulas of this invention analogous to N-containing heterocycles.

"Alkoxy", "cycloalkoxy", "aryloxy", "arylalkyloxy", "oxy heterocycle", "thioalkyl", "thiocycloalkyl", "arylthio", and "arylalkylthio" means substituents wherein an alkyl, cycloalkyl, aryl, or arylalkyl, respectively, are attached to an oxygen atom or a sulfur atom through a single bond, such as but not limited to methoxy, ethoxy, propoxy, butoxy, thioethyl, thiomethyl, phenyloxy, benzyloxy, mercaptobenzyl.

"Halogen" means any atom selected from the group consisting of fluorine, chlorine, bromine and iodine.

Any substituent designation that is found in more than one site in a compound of this invention shall be independently selected.

When a group is stated to be substituted with "one or more" of another group, this typically means 1 to 3 substituents, ordinarily 1, 2 or 3 substitutents.

Those of skill in the art will also recognize that the compounds of the invention may exist in many different protonation states, depending on, among

other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state--any and all protonated forms of the compounds are intended to fall within the scope of the invention.

Amino Acids

"Amino-acid" refers to a radical derived from a molecule having the chemical formula H_2N–CHR^{28}–COOH, wherein R^{28} is a side group of a naturally-occurring or known synthetic amino-acid. The amino acids optionally are substituted with hydrocarbon typically of 1 to 8 carbons at one or more carboxyl or amino groups, whether those groups are on the side chain or are free after linking the amino acid to the remainder of the compound of this invention.

Optionally the amino acid residue is a hydrophobic residue such as mono- or di-alkyl or aryl amino acids, cycloalkylamino acids. Optionally, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included.

Generally, only one of any site in the parental molecule is substituted with an amino acid, although it is within the scope of this invention to introduce amino acids at more than one permitted site. In general, the alpha-amino or alpha-carboxyl group of the amino acid are bonded to the remainder of the molecule, i.e., carboxyl or amino groups in the amino acid side chains generally are not used

The compounds of this invention are useful as linkers, spacers or affinity (typically hydrophobic) moieties in preparing affinity absorption matrices. The compounds of the invention optionally are bound covalently to an insoluble matrix and used for affinity chromatography separations, depending on the nature of the groups of the compounds, for example compounds with pendant aryl groups are useful in making hydrophobic affinity columns.

They also are useful as linkers and spacers in preparing immobilized enzymes for process control, or in making immunoassay reagents. The compounds herein contain functional groups that are suitable as sites for cross-linking desired substances. For example, it is conventional to link affinity reagents such as hormones, peptides, antibodies, drugs, to insoluble substrates. These insolublized reagents are employed in known fashion to absorb binding partners for the affinity reagents from manufactured preparations, diagnostic samples and other impure mixtures. Similarly, immobilized enzymes are used to perform catalytic conversions with facile recovery of enzyme. Bifunctional compounds are commonly used to link analytes to detectable groups in preparing diagnostic reagents.

The compounds of this invention are labeled with detectable moieties such biotin, radioisotopes, enzymes for diagnostic purposes. Suitable techniques for accomplishing the labeling of the compounds of the formulas of this invention are well known and will be apparent to the artisan from consideration of this specification as a whole. For example, one suitable site for labeling is R^{17} or R^{19}.

More typically, however, the compounds of the invention are employed for the treatment or prophylaxis of viral infections such as yellow fever virus, Dengue virus, hepatitis B virus, hepatitis G virus, Classical Swine Fever virus or the Border Disease Virus, but more particularly Flaviviral or Picornaviral infections, in particular, HCV and BVDV.

The therapeutic compound(s) of this invention are administered to a subject mammal (including a human) by any means well known in the art, i.e.

orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization. The therapeutically effective amount of the compound(s) is a Flaviviral or Picornaviral growth inhibiting amount. More preferably, it is a Flaviviral or Picornaviral replication inhibiting amount or a Flaviviral or Picornaviral enzyme inhibiting amount of the compounds of the formulas of this invention. This is believed to correspond to an amount which ensures a plasma level of between about 1μg/ml and 100 mg/ml, optionally of 10 mg/ml. This optionally is achieved by administration of a dosage of in the range of 0.001 mg to 60 mg, preferably 0.01 mg to 10 mg, preferably 0.1 mg to 1 mg per day per kg bodyweight for humans. These are starting points for determining the optimal dosage of the compound of this invention. The actual amount will depend upon many factors known to the artisan, including bioavailability of the compound, whether it contains a prodrug functionality, its metabolism and distribution in the subject and its potency, among others. It typically is necessary to determine the proper dosing in the clinical setting, and this is well within the skill of the ordinary artisan. The therapeutically effective amount of the compound(s) of this invention optionally are divided into several sub-units per day or are administered at daily or more than one day intervals, depending upon the pathologic condition to be treated, the patient's condition and the nature of the compound of this invention.

As is conventional in the art, the evaluation of a synergistic effect in a drug combination may be made by analyzing the quantification of the interactions between individual drugs, using the median effect principle described by Chou et al. in *Adv. Enzyme Reg.* (1984) 22:27 or tests such as, but not limited to, the isobologram method, as previously described by Elion et al. in *J. Biol. Chem.* (1954) 208:477-488 and by Baba et al. in *Antimicrob. Agents Chemother.* (1984) 25:515-517, using EC_{50} for calculating the fractional inhibitory concentration.

Suitable anti-viral agents for inclusion in combination antiviral compositions or for coadministration in a course of therapy include, for instance, interferon alpha, ribavirin, a compound falling within the scope of disclosure of EP 1162196, WO 03/010141, WO 03/007945, WO04/005286 and WO 03/010140, a

simultaneous, separate or sequential use in viral infection therapy, such as of HCV, BVDV and Coxsackie virus. Examples of such further therapeutic agents for use in combinations include agents that are effective for the treatment or prophylaxis of these infections, including interferon alpha, ribavirin, a compound faling within the scope of disclosure EP 1162196, WO 03/010141, WO 03/007945, WO04/005286 and WO 03/010140, a compound falling within the scope of disclosure WO 0/204425, and other patents or patent applications within their patent families or all the foregoing filings and/or an inhibitor of Flaviviral protease and/or one or more additional Flavivirus polymerase inhibitors.

When using a combined preparation of (a) and (b):

- the active ingredients (a) and (b) may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.
- the therapeutically effective amount of the combined preparation of (a) and (b), especially for the treatment of viral infections in humans and other mammals, particularly is a Flaviviral or Picornaviral enzyme inhibiting amount. More particularly, it is a Flaviviral or Picornaviral replication inhibiting amount of derivative (a) and a Flaviviral or Picornaviral enzyme inhibiting amount of inhibitor (b). Still more particularly when the said Flaviviral or Picornaviral enzyme inhibitor (b) is a polymerase inhibitor, its effective amount is a polymerase inhibiting amount. When the said Flaviviral or Picornaviral enzyme inhibitor (b) is a protease inhibitor, its effective amount is a protease inhibiting amount.
- ingredients (a) and (b) may be administered simultaneously but it is also beneficial to administer them separately or sequentially, for instance within a relatively short period of time (e.g. within about 24 hours) in order to achieve their functional fusion in the body to be treated.

The invention also relates to the compounds of the formulas of this invention being used for inhibition of the proliferation of other viruses than BVDV, HCV or Coxsackie virus, particularly for the inhibition of other

flaviviruses or picornaviruses, with in particular yellow fever virus, Dengue virus, hepatitis B virus, hepatitis G virus, Classical Swine Fever virus or the Border Disease Virus, and also for the inhibition of HIV and other retroviruses or lentiviruses.

More generally, the invention relates to the compounds of the formulas of this invention being useful as agents having biological activity (particularly antiviral activity) or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells remote from an animal.

Salts and Solvates

The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms formed by the compounds of the compounds of this invention. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid.

The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions).

The compounds of this invention include the solvates formed with the compounds of this invention and their salts, such as for example hydrates, alcoholates. The compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the compounds of this invention with one or more amino acids as described above. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a compound of this invention. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

The compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na+, Li+, K+, Ca+2 and Mg+2. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in

association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions).

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li+, Na+, Ca+2 and Mg+2 and K+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include, for instance, inorganic acids such as hydrohalogen acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, benzoic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, fumaric, tartaric, pyruvic, maleic, malonic, malic, salicylic (i.e. 2-hydroxybenzoic), *p*-aminosalicylic, isethionic, lactobionic, succinic oxalic and citric acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and *p*-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids,. C_1-C_6 alkylsulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic. Exemplary salts include mesylate and HCl.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX4+ (wherein X is C_1-C_4 alkyl). Physiologically acceptable salts

least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" contain undetectable levels of any other isomer.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), with asymmetric compounds bearing an acidic functionality, such as carboxylic acid and sulfonic acid.

The diastereomeric salts optionally are induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994). Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched

xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and Chiralpak™ AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane, modified with an alcohol such as ethanol, isopropanol. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990). "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

As used herein and unless otherwise stated, the term " enantiomer " means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "isomers" as used herein means all possible isomeric forms, including tautomeric and sterochemical forms, which the compounds of the formulas of this invention may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well.. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically

isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of the formulas of this invention may have at least one chiral center) of the basic molecular structure, as wel as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration.

Pure isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular, the term "stereoisomerically pure" or "chirally pure" relates to compounds having a stereoisomeric excess of at least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantionierically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional

crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and ChiralpakTM AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane, modified with an alcohol such as ethanol, isopropanol. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

The terms cis and trans are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents

on a ring moiety. The absolute stereochemical configuration of the compounds of formula (1) may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

Metabolites

The present invention also provides the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C14 or H3) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no antiviral activity of their own.

Formulations

The compounds of the invention optionally are formulated with conventional pharmaceutical carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers,

binders. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid.

Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or powders.

Suitable pharmaceutical carriers for use in the said pharmaceutical compositions and their formulation are well known to those skilled in the art, and there is no particular restriction to their selection within the present invention. They may also include additives such as wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, solvents, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or sodium chloride), provided the same are consistent with pharmaceutical practice, i.e. carriers and additives which do not create permanent damage to mammals. The pharmaceutical compositions of the present invention may be prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps procedure, with the selected carrier material. Where appropriate, the other additives such as surface-active agents are prepared by micronisation, for instance in view to obtain them in the form of microspheres usually having a diameter of

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with poylypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from I to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol - polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C_8-C_{22} alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

A more detailed description of surface-active agents suitable for this purpose may be found for instance in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Crop., Ridgewood, New Jersey, 1981), "Tensid-Taschenbucw', 2 d ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants, (Chemical Publishing Co., New York, 1981).

compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polymethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and mixtures thereof.

In view of the fact that, when several active ingredients are used in combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient,

e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Suitable methods for drug delivery include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and mixtures thereof.

Several active ingredients used in combination may not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated. Thus, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient, e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Exemplary Enumerated Compounds

Embodiments of the invention are named below in tabular format (Table 7). Each embodiment of Table 7 is depicted as a substituted nucleus (Sc) in which the nucleus is designated by a number and each substituent is designated in order by further numbers. Table 1 is a schedule of nuclei used in forming the embodiments of Table 7. Each nucleus (Sc) is given a number designation from Table 1, and this designation appears first in each embodiment name. Similarly, Tables 2, 3, 4, 5 and 6 list the selected substituents, again by number designation.

Accordingly, each named embodiment of Table 7 is depicted by a number designating the nucleus from Table 1. If the nucleus is of formula 1 (from Table

Exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations, and are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, workup procedures, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Workup typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

General aspects of these exemplary methods are described below. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsecquent processes.

The terms "treated", "treating", "treatment", mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in

such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic sysnthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modification of the exemplified schemes and examples leads to various analogs of the specific exemplary materials produced above. The above citations describing suitable methods of organic synthesis are applicable to such modifications.

In the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid

chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. Such separations are desireable if addition reactions place substituents at both of the pyrimidine nitrogen atoms. Separation of these isomers is well within the skill of the artisan.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

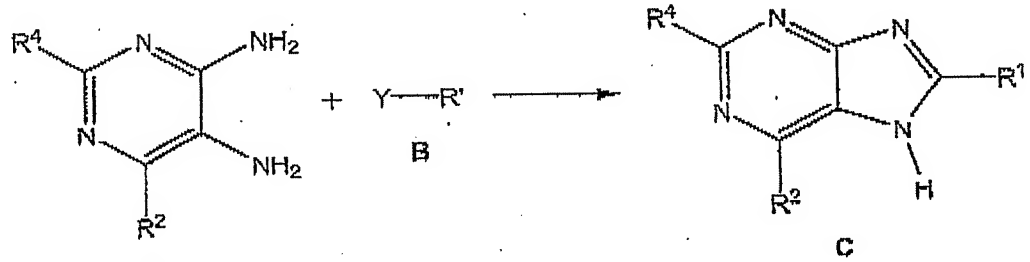
Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction. One skilled in the art will apply techniques most likely to achieve the desired separation.

A synthetic route to 5-benzyl-2-phenyl-5H-imidazo[4,5-d]pyrimidine and analogues is shown in Scheme A.

Compounds of the invention also are conveniently prepared by a two step process. First, a (substituted) 3,4-diaminopyrimidine (A) is reacted with B to give imidazo[4,5-d]pyrimidines C (Scheme 1). If Y is COOH, then the cyclization is carried out under acidic catalysis (preferably in polyphosphoric acid at a temperature between 90 and 200°C); other methods include reaction in 4N hydrochloric acid at reflux temperature or neat at a temperature between 90 and 180°C (for aliphatic carboxylic acids). In the case of acid-sensitive groups like alkoxy or thiophene, the reaction can be carried out in phosphorus oxychloride at a temperature between 70 and 120°C. Alternatively, reaction with aldehydes (Y = CHO) or their bisulfite adducts under oxidative conditions (nitrobenzene, DDQ, copper(II)acetate, O_2, sulfur) gives imidazo[4,5-d]pyrimidines C. Other methods are the reaction of (substituted) 3,4-diaminopyrimidines (A) with orthoesters (Y = $C(OR)_3$), anhydrides (Y = OCOOR) or acid halogenides (Y = COX).

Further methods for the preparation of the compounds of the invention are set forth in Schemes 1-5 below.

Scheme 1:

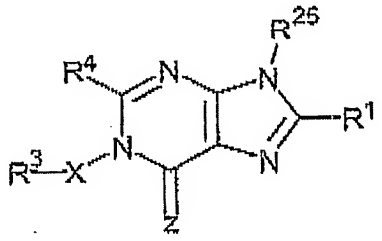


The imidazo[4,5-d]pyrimidines C are present in four tautomeric forms (1*H*, 3*H*, 4*H*, 6*H*).

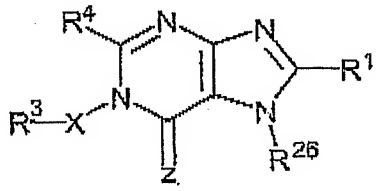
Substituents, for example R^2 and R^4, are introduced by two ways: i) by cylization of an appropiately substituted 3,4-diaminopyrimidine or ii) by

This mixture can be separated by column chromatography (silica gel, eluent: mixture of dichloromethane and methanol). The structures of the isolated components can then be assigned by NMR spectroscopy by single crystal x-ray analysis.

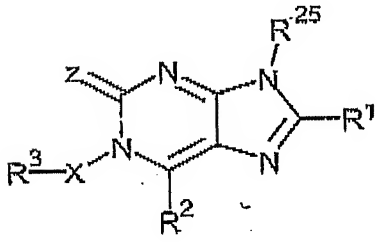
Alternatively, the crude reaction mixture can be recrystallized from an appropiate solvent (mixture), e.g. from a mixture of diisopropyl ether and ethyl acetate, to give the pure alkylated products.



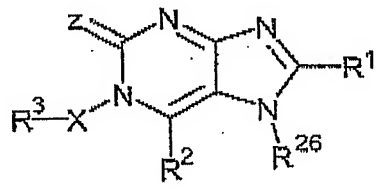
E



F



G



H

Compounds of general structure E, F, G and H can be prepared by alkylation (for example with (cyclo)alkylbromide or (cyclo)alkyliodide) of the corresponding compounds where Z=O, Z=S or Z=NR or their isomers. The resulting mixtures can be separated by column chromatography. The required starting materials are, for example, prepared from the corresponding chloro-analogues by nucleophilic substitution, or by ether cleavage of the corresponding alkoxy analogues.

chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. Such separations are desireable if addition reactions place substituents at both of the pyrimidine nitrogen atoms. Separation of these isomers is well within the skill of the artisan.

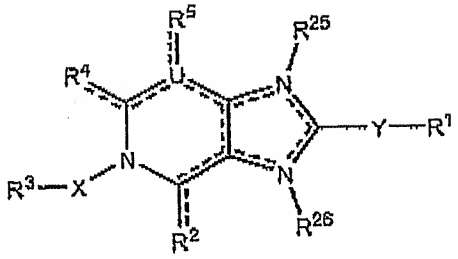
Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX).

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction. One skilled in the art will apply techniques most likely to achieve the desired separation.

A synthetic route to 5-benzyl-2-phenyl-5H-imidazo[4,5-d]pyrimidine and analogues is shown in Scheme A.

We Claim:

1. A compound of formula (A)



(A)

wherein:

the dotted lines represent optional double bonds, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

U is N;

R^1 is selected from hydrogen, aryl, heterocycle, C_1-C_{10} alkoxy, C_1-C_{10} thioalkyl, C_1-C_{10} alkyl-amino, C_1-C_{10} dialkyl-amino, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and C_{4-10} cycloalkynyl, wherein each are optionally substituted with 1 or more R^6;

Y is selected from a single bond, O, S(O)m (where m is an integer from 0 to 2), NR^{11}, C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene, or C_{1-10} alkylene, C_{2-20} alkenylene or C_{2-10} alkynylene, wherein 1 to 3 methylene groups optionally are independently replaced by 1 to 3 heteroatoms selected from O, S or NR^{11};

R^2 and R^4 are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, $-NO_2$, $-NR^7R^8$, haloalkyloxy, haloalkyl, $-C(=O)R^9$, $-C(=S)R^9$, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-16} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, and heterocycle, provided that when one of R^{25} or R^{26} is present, then either R^2 or R^4 is selected from =O, =S, or $=NR^{27}$;

X is selected from C_1-C_{10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, where each may include one or more heteroatoms selected from O, S, or NR^{11}, provided any such heteroatom is not adjacent to the N in the ring;

R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R^{10})-, or heterocycle, where each said substituent is optionally substituted with at least one R^{17}, provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO_2, -NR^7R^8, haloalkyloxy, haloalkyl, -C(=O)R^9, -C(=O)OR^9, -C(=S)R^9, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, and heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl, -CO_2R^{18}, NO_2, -NR^7R^8, C_{1-18} haloalkyl, C(=O)R^{18}, C(=S)R^{18}, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, and C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19};

R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, heterocycle, -C(=O)R^{12}; -C(=S) R^{12}, an amino acid residue linked through a carboxyl group thereof, and the group formed when R^7 and R^8 are taken together with the nitrogen to form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{1-18} alkoxy, -$NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, and an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, arylalkyl (unsubstituted, or substituted with $C(O)OR^{18}$), C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{17} is independently selected from the group consisting of (a) hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halogenated alkyl, C_{2-18} halogenated alkenyl, C_{2-18} halogenated alkynyl, C_{1-18} halogenated alkoxy, C_{1-18} halogenated alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, CO_2H, CO_2R^{18}, NO_2, NR^7R^8, haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, heterocycle, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle and C_{1-18} hydroxyalkyl, where each of said aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle, or C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19}, and (b) M-Q- wherein M is a ring optionally substituted with 1 or more R^{19}, and Q is a bond or a linking group connecting M to R^2 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with 1 or more R^{19};

R^{19} is selected from

(a) H;

(b) NO_2, SH, $NR^{20}R^{21}$, OH, halogen and CN;

(c) Sulfone, sulfonamide and sulfoxide;

(d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle, and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, and $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH;

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and arylC_{1-18} alkyl; and

salts, tautomers, polymorphs, isomers and solvates thereof.

2. The compound of claim 1 wherein R^1 is haloaryl, X is methylene, R^3 is heterocycle substituted with 1 or 2 R^{17}.

3. The compound of claim 1 wherein R^1 is an aryl or aromatic heterocycle substituted with 1 or 2 R^6.

4. The compound of claim 1 wherein R^3 is heterocycle.

5. The compound of claim 1 wherein YR^1 is haloaryl.

6. The compound of claim 5 wherein haloaryl is ortho-fluorophenyl.

7. The compound of claim 1 wherein R^3 is isoxazolyl substituted with 1 R^{17}.

8. The compound of claim 2 wherein R^{17} is aryl or an aromatic heterocycle which is substituted with 1, 2 or 3 R^{19}.

9. The compound of claim 1 wherein YR^1 is none of hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl.

10. The compound of claim 9 wherein YR^1 is not hydrogen or C_{1-6} alkyl.

11. The compound of claim 1 wherein R^{19} is trihalomethyl, trihalomethoxy, alkoxy or halogen.

12. The compound of claim 1 wherein R^1 is aryl or aromatic heterocyle substituted with 1, 2 or 3 R^6 wherein R^6 is halogen, C_{1-18} alkoxy; or C_{1-18} haloalkyl.

13. The compound of claim 12 wherein R^1 is phenyl substituted with 1, 2 or 3 halogens.

14. The compound of claim 13 wherein halogen is fluoro.

15. The compound of claim 1 wherein Y is a single bond, O, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene or one of said groups containing 1 to 3 heteroatoms selected from O, S or NR^{11}.

16. The compound of claim 15 wherein Y is $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-5}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}$ or C_{3-10} cycloalkylidene.

17. The compound of claim 15 wherein Y is $-OCH_2-$, $-CH_2O-$, C_{1-2} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, O or a bond.

18. The compound of claim 15 wherein Y is a bond.

19. The compound of claim 1 wherein YR^1 is a single ring aromatic carbocycle or a heterocycle containing 1 or 2 N, S or O atoms in the ring.

20. The compound of claim 19 wherein the carbocycle or heterocycle contains 4 to 6 ring atoms.

21. The compound of claim 1 wherein YR^1 is halo- or halomethyl-substituted phenyl.

22. The compound of claim 1 wherein aryl or heteroaryl are substituted ortho or meta with halo- or halomethyl.

23. The compound of claim 1 wherein X is selected from the group consisting of alkylene, alkynylene or alkenylene and said hydrocarbons having an intrachain N, O or S heteroatom.

24. The compound of claim 1 wherein X is alkylene.

25. The compound of claim 23 wherein X is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene and C_{2-6} alkynylene.

26. The compound of claim 1 wherein X is methylene.

27. The compound of claim 1 wherein R^5 is aryl or a heterocycle substituted with 0 to 3 R^{17}.

28. The compound of claim 27 wherein the heterocycle is an aromatic heterocycle.

29. The compound of claim 28 wherein the heterocycle contains 1, 2 or 3 N, S or O atoms in the ring, is linked to X through a ring carbon atom and contains 4 to 6 total ring atoms.

30. The compound of claim 29 wherein R^5 is isoxazolyl substituted with 1 to 3 R^{17}.

31. The compound of claim 1 wherein R^{17} is aryl or a heterocycle further substituted with 1 to 3 R^{19}.

32. The compound of claim 1 wherein M is aryl or aromatic heterocycle.

33. The compound of claim 1 wherein Q contains 0 to 20 atoms selected from C, O, S, N and H.

34. The compound of claim 1 wherein M is a cyclic group selected from R^{17}

35. The compound of claim 1 wherein R^{17} is selected from the group consisting of C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl; arylalkyloxy; arylalkylthio; heterocycle; C_{1-18} hydroxyalkyl, each of said C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl; arylalkyloxy; arylalkylthio; heterocycle; and C_{1-18} hydroxyalkyl is unsubstituted or is substituted 1 or more R^{19}

36. The compound of claim 1 wherein R^{17} is selected from the group consisting of aryl and heterocycle, and where said aryl or heterocycle is optionally substituted with 1 or more R^{19}.

37. The compound of claim 1 wherein R^9 and R^{10} are H, OH or alkyl.

38. The compound of claim 1 wherein R^5 is H.

39. The compound of claim 1 wherein R^6 is halogen.

40. The compound of claim 1 wherein R^7, R^8, R^{10}, R^{11}, R^{15}, R^{16}, R^{20}, and R^{21} are independently H or C_{1-18} alkyl.

41. The compound of claim 1 wherein R^{12} is OH or alkyl.

42. The compound of claim 1 wherein R^{19} is selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; alkenyloxy; alkynyloxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; halogen; OH; CN; cyanoalkyl; NO_2; $NR^{20}R^{21}$; haloalkyl; haloalkyloxy; $C(=O)R^{18}$; $C(=O)OR^{18}$; $OalkenylC(=O)OR^{18}$; $-OalkylC(=O)NR^{20}R^{21}$; aryl; heterocycle; $-OalkylOC(=O)R^{18}$; $C(=O)N(C_{1-6}$ alkyl), $N(H)S(O)(O)(C_{1-6}$ alkyl); arylalkyloxy; aryloxy; arylalkyloxy; and arylalkyl.

43. The compound of claim 42 wherein R^{19} is independently selected from the group consisting of halogen, $N(R^{20}R^{21})$, alkoxy, halo-substituted alkyl and halo-substituted alkoxy.

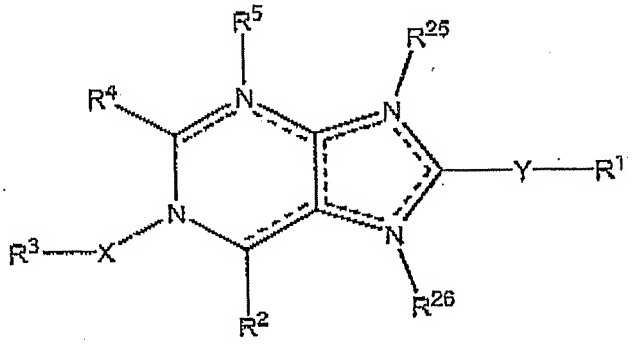
44. The compound of claim 1 wherein R^{25} and R^{26} are not present.

45. The compound of claim 1 which is not substituted at R^{25} but is substituted at R^{26}, and either R^2 or R^4 is selected from (=O), (=S), and (=NR^{27}).

46. The compound of claim 1 wherein haloalkyl or haloalkyloxy is $-CF_3$ or $-OCF_3$.

47. The compound of claim 1 wherein R^{19} is any individual, combination or subcombination of substituents (a) – (k).

48. A compound having the general formula (A),



(A)

wherein:

the dotted lines represent optional double bonds, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

R^1 is selected from hydrogen, aryl, heterocycle (other than piperazinyl, piperidinyl, or either substituted with 1 or more R^6), C_1-C_{10} alkoxy, C_1-C_{10} thioalkyl,

C_1-C_{10} alkyl-amino, C_1-C_{10} dialkyl-amino, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, and C_{4-10} cycloalkynyl, wherein each are optionally substituted with 1 or more R^6;

Y is selected from a single bond, O, S(O)m (where m is an integer from 0 to 2), NR^{11}; C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, or C_{1-10} alkylene, C_{2-20} alkenylene or C_{2-10} alkynylene wherein 1 to 3 methylene groups optionally are independently replaced by 1 to 3 heteroatoms selected from O, S or NR^{11}; provided, however, that YR^1 is not H;

R^2 and R^4 are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO_2, -NR^7R^8, haloalkyloxy, haloalkyl, -C(=O)R^9, -C(=S)R^9, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle, provided that when one of R^{25} or R^{26} is present, then either R^2 or R^4 is selected from (=O), (=S), and =NR^{27}; and further provided that not both of R^2 and R^4 is OH, SH, thio or oxo;

X is selected from C_1-C_{10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, where each may include one or more heteroatoms selected from O, S, or NR^{11}, provided any such heteroatom is not adjacent to the N in the ring;

R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R^{10})-, or heterocycle, where each said substituent may be optionally substituted with at least one R^{17}, provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO_2, -NR^7R^8, haloalkyloxy, haloalkyl, -C(=O)R^9, -C(=O)OR^9, -C(=S)R^9, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl,

$-CO_2R^{18}$, NO_2, $-NR^7R^8$, C_{1-18} haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19};

R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, heterocycle, $-C(=O)R^{12}$; $-C(=S)R^{12}$, an amino acid residue linked through a carboxyl group thereof, or where R^7 and R^8 together with the nitrogen form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{1-18} alkoxy, $-NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, or $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, or an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{17} is independently M-Q- wherein M is a ring optionally substituted with 1 or more R^{19}, and Q is a bond or a linking group connecting M to R^3 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with 1 or more R^{19};

R^{19} is selected from

(a) H;

(b) NO_2, SH, $NR^{20}R^{21}$, OH, halogen and CN;

(c) Sulfone, sulfonamide and sulfoxide;

(d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, or $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH; and

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and aryl C_{1-18} alkyl, and

salts, tautomers, polymorphs, isomers and solvates thereof.

49. The compound of claim 48 wherein Y is a single bond, and R^1 is aryl or aromatic heterocycle which is unsubstituted or substituted with one or more R^6.

50. The compound of claim 48 wherein X is C_1-C_{10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene.

51. The compound of claim 48 wherein R^3 is heterocyle.

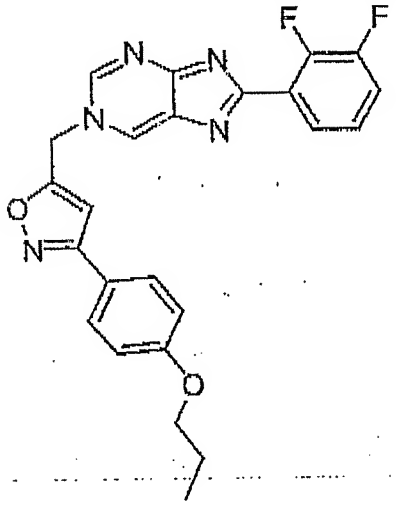
52. The compound of claim 48 wherein R^3 is heterocycle substituted with R^{17} where Q is a bond and M is aryl substituted with 1 or 2 R^{19}.

53. The compound of claim 48 wherein Y is a single bond, and R^1 is phenyl.

54. The compound of claim 48 wherein R^3 is isoxazole substituted with R^{17} where Q is a bond and M is aryl substituted with 1 or 2 R^{19}.

55. The compound of claim 48 wherein R^3 is isoxazole substituted with R^{17} where Q is a bond and M is phenyl substituted with 1 or 2 R^{19}.

56. A compound having the structure

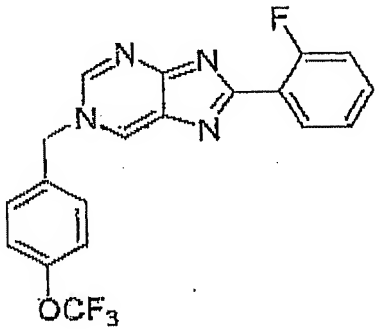


and its salts, tautomers, polymorphs and solvates.

57. 8-(2-Fluorophenyl)-1-[(4-trifluoromethyl)phenylmethyl]-1*H*-purine and its salts, tautomers, polymorphs and solvates.

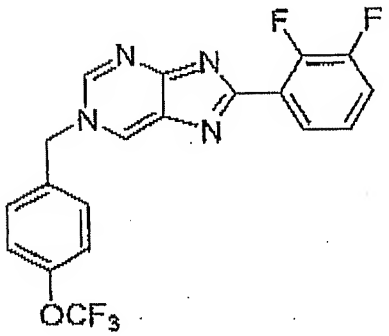
58. 1-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-8-(2,3-difluorophenyl)-1H-purine and its salts, tautomers, polymorphs and solvates.

59. The compound



and its salts, tautomers, polymorphs and solvates.

60. A compound of the structure



and its salts, tautomers, polymorphs and solvates.

61. A composition comprising a pharmaceutically acceptable excipient and a compound of claims 1, 48, and 64-70.

62. A method comprising administering to a subject in need of treatment or prophylaxis of a viral infection an antivirally effective amount of a composition of claim 61.

63. The method of claim 62, wherein the viral infection is an HCV infection.

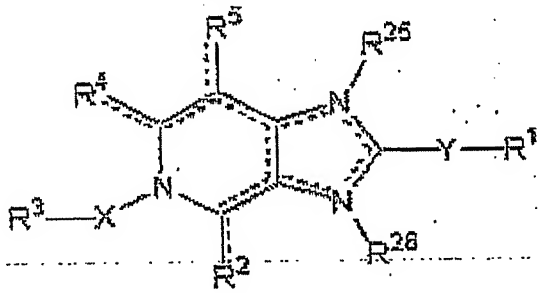
64. The method of claim 63 further comprising administering at least one additional antiviral therapy to the subject.

65. The method of claim 64 wherein the additional therapy is is selected from the group consisting of an interferon alpha and ribavirin.

66. A method of screening antiviral compounds which comprises providing a compound of claims 1 or 48 and determining the anti-viral activity of said compound.

67. The method of claim 66 wherein said anti-viral activity is determined by the activity of said compound against one or more viruses belonging to the family of the Flaviviridae and/or of the Picornaviridae.

68. A method for structure-activity determination of analogues of compounds of WO 2004/005286 having the general structure



wherein the R, X and Y groups are defined in WO 2004/005286, comprising

(A) preparing an analogue of a compound falling within the scope of WO 2004/005286 wherein C_7 is replaced by N; and

(B) determining the anti-HCV activity of the compound of step (A).

69. The method of claim 68 wherein the substituent is located at R^3, R^2, R^4, R^{2b} and/or R^1.

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle, and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, and $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH;

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and arylC_{1-18} alkyl; and

salts, tautomers, polymorphs, stereoisomers and solvates thereof.

2. The compound of claim 1 wherein R^1 is haloaryl, X is methylene, R^3 is heterocycle substituted with 1 or 2 R^{17}.

3. The compound of claim 1 wherein R^1 is an aryl or aromatic heterocycle substituted with 1 or 2 R^6.

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, or $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH; and

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and aryl C_{1-18} alkyl, and

salts, tautomers, polymorphs, stereoisomers and solvates thereof.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference K2500-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/BE 03/00117	International filing date *(day/month/year)* 03.07.2003	Priority date *(day/month/year)* 03.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D471/04		
Applicant K.U. LEUVEN RESEACH & DEVELOPMENT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 32 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.01.2004	03.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Boletti-Cremers, K Telephone No. +49 89 2399-8541

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BE 03/00117

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 4-12, 15, 16, 19-126	as originally filed
3A, 3B, 13A, 13B, 14A, 14B, 17A, 17B, 18A, 18B	filed with telefax on 09.07.2004

Claims, Numbers

1-22	filed with telefax on 09.07.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 20

   because:

   ☒ the said international application, or the said claims Nos. 20 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 7-14 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 7-14 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 7-14

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	7
Inventive step (IS)	Yes:	Claims	1-7 (with proviso)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19, 21,22
	No:	Claims	

2. Citations and explanations

see separate sheet

POINT I.

1. Present claim 7 does not satisfy the requirements of Art 34 (2) (b) , last sentence PCT .

a. Indeed , several disclaimers which were present at the origin and which encompassed various compounds or teachings of compounds , namely the compounds summarised at **original** page 134, lines 31-34 , the teachings of compounds recited at **original** page 135, lines 1-7, and page **original** page 135 , lines 22-27 , are no longer present in present amended claim 7 which now implicitly extends its scope so as to encompass them. Those not recited compounds should possibly enter that claim (they are still in the description on page 11 and 12....) , bearing the following point III in mind.

b. Present objection applies "mutatis mutandis", if necessary, to the descriptive amendments submitted on 09.07.04 by the Applicant.

2. New claim 11 cannot be accepted on the basis of the support pointed out by the Applicant on 09.07.04. Said support (page 14,lines 15-19) not being clear and unambiguous, claim 11 is not allowable.

POINT III.

1 The use of the multiple disclaimers in present claim 7 renders said claim obscure in scope in that the desired extension of protection is not clearly delimited towards the content of the prior art and , since the ISA could not perform a search covering all the claimed alternatives of the possible compounds (A) on file, the IPEA invites the Applicant to restrict claim 7 so as to enable a clear and unambiguous acknowledgment of the novelty towards the prior art as well as a possible search which would encompass all the claimed possibilities of that claim, which has not yet extensively been searched at present .

Indeed , present communication does not deal with the examination of the full extension of the protection set out in the compound claims on file, because the ISA could not perform a search covering all the claimed alternatives of the possible compounds A on file.

Consequently to the above , no meaning opinion could be given for the 2 reasons that claim 7 is obscure and not sufficiently supported by the description, and that it has not yet been extensively searched.
A further search will possibly be performed in the European proceedings , provided that

the compound claims could be rendered clear in scope , **first.**

2 For the assessment of the presently worded claim 20 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a new medical treatment.

POINT V.

The following documents , quoted in the I.S.R., have been considered as relevant for the examination of the present application . Their numbering will be adhered to for the rest of the procedure.

(1) GB-A-2 158 440.
(2) Khimiko-Farmatsevtichsskii Zhurnal, vol. 23, no. 1, 1989, pages 56-9 **(copy provided).**
(3) HU-A-78 019 *.
(4) WO-A-99 27929.
(5) WO-A-96 11192, cited in the application.
(6) WO-A-96 12703, cited in the application .
(7) US-A-5 302 601, cited in the application.
(8) EP-A-344 414.
(9) WO-A-95 16687.
(10) Journal of the Combinatorial Chemistry, vol. 4, no. 5, 2002, pages 475-483. (point VI)

* The IPEA is grateful to the Applicant for the provision of a copy of (3).

1. Novelty.

1.1 The content of (1) does not affect the novelty of the claims on file in that the examples of (1) do not fall within the scope of the compound and use claims on file.

1.2 Although (2) and (3) are enabling disclosures for the purpose of the examination of the novelty of the claimed matter on file, the IPEA is not familiar with the languages

used in those documents and invites the Applicant to possibly provide a copy of the translations of those documents into one of the official languages of the regional European proceedings to come.

1.3 In view of the fact that example 4 of (4) has been disclaimed from the scope of claim 7 by means of the disclaimer at page 10, line 8 of the claims , the novelty vis à vis of the content of (4) can be acknowledged. However , no descriptive amendment concerning that compound has been submitted. Therefore there is a discrepancy between claim 7 and the description now, which should be dealt with in the European regional proceedings.

1.4 In view of the fact that the all the compounds of (5) have now been withdrawn from claim 7 on file (see page 10, lines 8-14) , that claim can be regarded as novel with respect to the content of (5).

1.5 In view of the fact that compounds of examples 3, 12 (compound 5 only) and 18 of (6) have not apparently be properly disclaimed from claim 7 , previous objection which concerned the disclosure of (6) , still require the Applicant's attention .
The compounds named previously should be avoided from at least claim 7 on file in the regional proceedings to come.

1.6 In response to previous absence of novelty with respect to the contents of (7) and (8) , the Applicant has now excluded the entire teachings set out in (7) and (8) to define those compounds , as now on page 8, lime 34 up to page 9 line 19 of present claim 7, on the basis of the support mentioned on page 17, lines 24-27 of the original description.
Even if this support can be accepted, the Applicant is invited to **restrict** said claim in the regional proceedings to come, in a way that a clear and unambiguous acknowledgement of the novelty vis à vis (7) and (8) could be enabled (see previous point III in this respect).

1.7 In view of the fact that the indolyle compounds of (9) do not fall within the scope of present claims 7 and following , the claimed matter on file can be regarded as novel with respect to the content of (9).

Indeed , even if attached though a linker to a possible imidazo (4,5-c) pyridine derivative , the indolyl substitution is not part of the possible definitions of the R^3 defined radicals associated to the claimed compounds on file.

Presumably , the reasons why Applicant deleted the compound named at original claim 7 , page 135 , lines 22-23 as a disclaimer from present claim 7 is related to present acknowledgement, and it requires further clarification.
If their is a correlation between the present absence of that compound in present claim 7 and the fact that the indolyle definitions are not encompassed under the possible definitions of R^3 radicals, previous point I a. is partially met because the original disclaimer which concerned that compound was not necessary and lead to an unnecessary additional lack of clarity of original claim 7.

1.8 Whether the content of (10) (refer especially to compounds 15 and 16 mentioned in scheme 4 on page 479 ; see also page 480,Table 4 in this respect) is relevant for the examination of the novelty of the claimed compounds on file will only be investigated in the European regional phase and will essentially depend on the examination of validity of the priority rights claimed by present invention , which at present is not possible.

2. Inventiveness.

In view of the fact that the claimed compounds possess one more unsaturation than the compounds disclosed in (1), they cannot be interpreted as the result of a non inventive selection of the antiviral compounds disclosed in (1) and in this respect , the IPEA acknowledges the inventiveness of the claimed matter on the basis of the Applicant' argumentation of 09.07.2004, provided that a clear acknowledgment of the novelty could be enabled in the regional proceedings to come.
It should also be added that present opinion is based on a partial search report and could be amended after the issue of an additional search report in the regional proceedings to come.

3. Formal Points.

3.1 The descriptive support pointed out by the Applicant in response to previous point 3.1 of the first preliminary opinion cannot be accepted as an answer to the invitation to give the reasons of the various disclaimers of claim 7.

Said objection is maintained and the Applicant is invited to give the **technical** reasons (thus the reasons starting from the prior art in general-some disclaimers are understood , some of them cannot be related to any of the prior art pieces provided

by the ISR-) of the existence of the provisos which are encompassed in claim 7 .

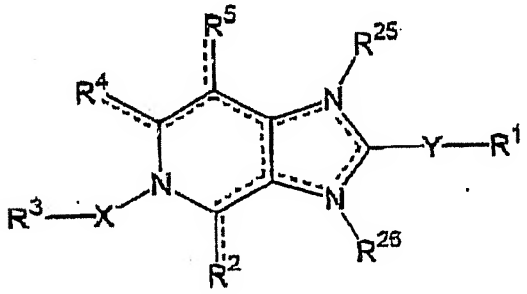
If those provisos are related to prior art which was not quoted in the ISR, he is also invited to name it, quote it in the description , and possibly already discuss their/its content(s) when the application will enter the regional proceedings to come.

3.2 Moreover the use of the multiple disclaimers in present claim 7 renders said claim is unclear in scope in that the desired extension of protection is not clearly delimited towards the content of the prior art , even if that prior art ((2)-(9)) does not affect the inventiveness of the claims on file .
Since present application deals mainly with the further use of known compounds which were already known for their possible therapeutical uses , as illustrated in the documents (2)-(9), possibly claim 7 should be deleted and replaced by an inventive (unamended) claim 1 where all the definitions could remain unchanged.
Under those circumstances no additional search should be provided because claim 1 was apparently searched by the ISA.
Indeed , present IPER does not deal with the examination of the full extension of the protection set out in the compound claims on file because the ISA could not perform a search covering all the claimed alternatives of the possible compounds (I) on file.

amended claims PCT/BE03/00117 : clean copy

CLAIMS

1. Use of a imidazo[4,5-c]pyridine derivative of the formula (Z), or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment or prevention of viral infections,



(Z)

wherein:

- the dotted lines represent an optional double bond, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;
- R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6, heterocyclic ring unsubstituted or substituted with one or more R^6, C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6;
- Y is selected from the group consisting of a single bond , O; $S(O)_m$; NR^{11}; and a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain, said heteroatoms being selected from the groups consisting of O, S, and N; such as C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}-$and C_{3-10} cycloalkylidene;
- each R^2 and R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 -or 6 membered heterocyclic, oxyheterocyclic or

thioheterocyclic ring; or, when one of R^{25} or R^{26} is different from hydrogen, either R^2 or R^4 is selected from (=O), (=S), and (=NR^{27});

- X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example –CH_2-, -$CH(CH_3)$-, -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2), -$(CH_2)_{2-4}$-O-$(CH_2)_{2-4}$-, -$(CH_2)_{2-4}$-S-$(CH_2)_{2-4}$-, -$(CH_2)_{2-4}$-NR^{10}-$(CH_2)_{2-4}$-, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as -CH=CH-CH_2-), C_{2-6} alkynylene;
- m is any integer from 0 to 2;
- R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl-NR^{10}-; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;; and each of said aryl, aryloxy, arylthio, aryl-NR^{10}-, 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring is optionally substituted with one or more R^{17}; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;
- R^5 is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; C(=O)R^9; C(=S)R^9; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;
- each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; C(=O)R^{18}; C(=S)R^{18}; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19};
- each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocyclic ring;

$C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof; alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocyclic ring;

- each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;
- each R^{10} and R^{11} is independently selected from the group the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocyclin ring; an amino acid residue linked through a carboxyl group thereof;
- R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through an amino group thereof;
- each R^{13} and R^{14} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof;
- each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through a carboxyl group thereof.
- R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2; $NR^{20}R^{21}$; OCF_3; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6}$ alkyl), $N(H)S(O)(O)(C_{1-6}$ alkyl); aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring each unsubstituted or substituted with 1 or more halogens;
- each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;
- R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl, ; C_{4-10} cycloalkenyl;
- each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an

amino acid residue;

each R^{25} or R^{26}, are absent or selected from the group consisting of of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; (C_{3-8} cycloalkyl)-C_{1-3} alkyl; aryl, such as phenyl; 5 or 6 membered heterocyclic ring, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, (C_{3-8} cycloalkyl)-C_{1-3} alkyl, C_{5-10} bicycloalkyl, adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, oxybenzyl, and OH; and heterocyclic ring having 3 to 7 carbon atoms, preferably a saturated heterocyclic ring wherein the heteroatoms are S, S(O), or $S(O)_2$ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocyclic ring carbon atoms. Provided that either R^{25} or R^{26} is hydrogen. Typically R^{25} or R^{26} is cyclopentyl or cyclohexyl; provided that if the compound is substituted at R^{25} or R^{26}, either R^2 or R^4 is selected from (=O), (=S), and (=NR^{27}); and

R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl; aryl; arylalkyl, such as benzyl.

2. The use according to claim 1, wherein said viral infection is an infection of a virus belonging to the family of Flaviviridae.

3. The use according to claim 1, wherein said viral infection is an infection of a hepatitis-C virus.

4. The use according to claim 1, wherein said viral infection is an infection of a virus belonging to the family of the Picornaviridae.

5. The use according to claim 1, wherein said viral infection is an infection of a Coxsackie virus.

6. The use of claim 1, wherein said compound is selected from the group consisting of:

5-[(4-Bromophenyl)methyl]-2-(2-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine

5-[(4-Bromophenyl)methyl]-2-(2-pyridinyl)-5*H*-imidazo[4,5-c]pyridine

5-[(4-Bromophenyl)methyl]-2-(1-naphthalenyl)-5*H*-imidazo[4,5-c]pyridine

5-[(4-Bromophenyl)methyl]-2-[(phenylthio)methyl]-5*H*-imidazo[4,5-c]pyridine

5-[(4-Bromophenyl)methyl]-2-[3-(trifluoromethyl)phenyl]-5*H*-imidazo[4,5-c]pyridine

5

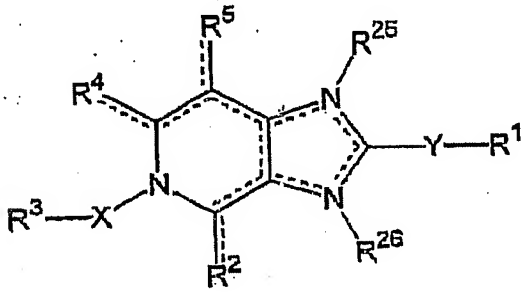
5-([1,1'-Biphenyl]-4-ylmethyl)-2-(2-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine

5-[(4-Chlorophenyl)methyl]-2-(2-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine

2-(2-Fluorophenyl)-5-[(4-iodophenyl)methyl]-5*H*-imidazo[4,5-c]pyridine

5-[[4-(1,1-Dimethylethyl)phenyl]methyl]-2-(2-fluorophenyl)-5H-imidazo[4,5-c]pyridine

7. An imidazo[4,5-c]pyridine compound according to formula A:



(A)

- or an enantiomer or a solvate, or a pharmaceutically acceptable salt thereof, wherein:

the dotted lines represent an optional double bond, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

- R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6, heterocyclic ring unsubstituted or substituted with one or more R^6, C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6

- Y is selected from the group consisting of a single bond , O; $S(O)_m$; NR^{11}; and a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain, said heteroatoms being selected from the groups consisting of O, S, and N; such as C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}-$and C_{3-10} cycloalkylidene;

- each R^2 and R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or

thioheterocyclic ring; or, when one of R^{25} or R^{26} is different from hydrogen, either R^2 or R^4 is selected from (=O), (=S), and (=NR^{27});

- X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example –CH_2-, -$CH(CH_3)$-, -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2), -$(CH_2)_{2-4}$-O-$(CH_2)_{2-4}$-, -$(CH_2)_{2-4}$-S-$(CH_2)_{2-4}$-, -$(CH_2)_{2-4}$-NR^{10}-$(CH_2)_{2-4}$-, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as -CH=CH-CH_2-), C_{2-6} alkynylene;

m is any integer from 0 to 2;

- R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl-NR^{10}-; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;; and each of said aryl, aryloxy, arylthio, aryl-NR^{10}-, 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring is optionally substituted with one or more R^{17}; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

- R^5 is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;

- each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^{18}$; $C(=S)R^{18}$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19};

- each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocyclic ring; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof; alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocyclic ring;

- each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;

- each R^{10} and R^{11} is independently selected from the group the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocyclin ring; an amino acid residue linked through a carboxyl group thereof;

- R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through an amino group thereof;

- each R^{13} and R^{14} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof;

each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through a carboxyl group thereof.

- R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2; $NR^{20}R^{21}$; OCF_3; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6}$ alkyl), $N(H)S(O)(O)(C_{1-6}$ alkyl); aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring each unsubstituted or substituted with 1 or more halogens;

-each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;

R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy;

$NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl, ; C_{4-10} cycloalkenyl;

-each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;

each R^{25} or R^{26}, are absent or selected from the group consisting of of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; (C_{3-8} cycloalkyl)-C_{1-3} alkyl;; aryl, such as phenyl; 5 or 6 membered heterocyclic ring, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, (C_{3-8} cycloalkyl)-C_{1-3} alkyl, C_{5-10} bicycloalkyl, adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, oxybenzyl, and OH; and heterocyclic ring having 3 to 7 carbon atoms, preferably a saturated heterocyclic ring wherein the heteroatoms are S, S(O), or $S(O)_2$ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocyclic ring carbon atoms. Provided that either R^{25} or R^{26} is hydrogen. Typically R^{25} or R^{26} is cyclopentyl or cyclohexyl; provided that if the compound comprises R^{25} or R^{26}, either R^2 or R^4 is selected from (=O), (=S), and ($=NR^{27}$); and

R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl; aryl; arylalkyl, such as benzyl;

with the proviso that:

-the substituents X, Y, R^1, R^2, R^3, R^4, R^5 are not a cephalosporin or wherein the substituents X, Y, R^1, R^2, R^3, R^4, R^5 are not an azabicyclo group, more particularly not 5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one;

-the compound is not 5-(2-piperidin-1-yl-ethyl)-2-(4-hydroxyphenyl)-1H-imidazo[4,5c] pyridin-5-ium bromide;

-the compound is not 4-[5-(2-{4-[Bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-ethyl)-5H-imidazo[4,5-c]pyridin-2-yl]phenol;

-the compound is not 4-[5-(3-{4-[Bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-propyl)-5H-imidazo[4,5-c]pyridin-2-yl]phenol;

-the compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[2-(5H-imidazo-[4,5-c]pyridin-5-yl)ethyl]thio]-phenol hydrate and/or 2,6-bis(1,1,-dimethylethyl)-4-[[2-(5H-imidazo-[4,5-c]pyridin-5-yl)propyl]thio]-phenol hydrate

-the compound is not a compound wherein XR^3 has the structure $-(CH_2)n-Y'-CO-N(R_1')(R_2')$ wherein R_1' and R_2' are each independently selected from hydrogen; straight

or branched chain alkyl of 1 to 15 carbon atoms; cycloalkyl having 3 to 8 carbon atoms; substituted cycloalkyl which can be substituted one or more by alkyl of 1 to 6 carbon atoms; bicycloalkyl having 3 to 8 carbon atoms in each ring; heterocyclicalkyl having 4 to 8 carbon atoms which can be optionally substituted by alkyl of 1 to 6 carbon atoms; heteroaromatic having 5 or 6 carbon atoms which can be optionally substituted by alkyl having 1 to 6 carbon atoms; phenyl; substituted phenyl which can be substituted one or more by a group independently selected from alkyl having 1 to 6 carbon atoms or halogen; straight or branched alkenyl having 3 to 15 carbon atoms with the proviso that the double bond of the alkenyl group cannot be adjacent to the nitrogen; cycloalkenyl having 5 to 8 carbon atoms with the proviso that the double bond cannot be adjacent to the nitrogen; and R_1' and R_2' cannot both be hydrogen; Y' is phenyl or phenyl substituted once or more than at one or more of the 2, 3, 5 or 6 positions of the phenyl ring by substituents independently selected from the group consisting of alkoxy having 1 to 6 carbon atoms; halogen wherein the halogen is selected from bromo, fluoro, or chloro; straight or branched chain alkyl having 1 to 6 carbon atoms; substituted straight or branched chain alkyl which can be substituted one or more by halogen; thioalkyl wherein the alkyl has 1 to 6 carbon atoms; alkoxyalkyl wherein the alkyl groups are each 1 to 6 carbon atoms; hydroxyalkyl wherein the alkyl has 1 to 6 carbon atoms; alkylthioalkyl wherein the alkyl groups are each 1 to 6 carbon atoms; cyano; mercaptoalkyl wherein the alkyl has 1 to 6 carbon atoms; hydroxy; amino; alkylamino wherein the alkyl group has 1 to 6 carbon atoms; and dialkylamino wherein the alkyl groups are each 1 to 6 carbon atoms; n is an integer of 1 to 5

-the compound is not 5-[2-(Biphenyl-4-yloxy)-ethyl]-5H-imidazo[4,5-c]pyridine;

-the compound is not 5-[2-(4-Phenoxy-phenoxy)-ethyl]-5H-imidazo[4,5-c]pyridine;

-the compound is not [5-(4-Fluorobenzyl)-5H-imidazo[4,5-c]pyridin-2-yl]-methylamine;

-the compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[3-(5H-imidazo-[4,5-c]pyridin-5-yl)propyl]thio]-phenol hydrate;

-the compound is not 5-[2-(4-Phenylmethyloxy-phenoxy)-ethyl]-5H-imidazo[4,5-c] pyridine;

-the compound is not 5-[3-(4-Phenoxy-phenoxy)-propyl]-5H-imidazo[4,5-c]pyridine

-the compound is not 5-{2-[4-(4-Fluorophenoxy)-phenoxy]-ethyl}-5H-imidazo[4,5-c] pyridine;

-the compound is not 5-[3-(4-Phenylmethyl-phenoxy)-propyl]-5H-imidazo[4,5-

c]pyridine;

the compound is not ((5-[4-(Fluorophenyl)methyl]-5-H-imidazo[4,5-c]-pyridine-2-yl) methyl)-carbamaat, methyl ester;

the compound is not 5-(4-Chlorophenylmethyl)-2-(piperidin-1-ylmethyl)-5H-imidazo[4,5-c]pyridine and its dihydrochloride salt;

the compound is not 5-(4-Chlorophenylmethyl)-2-(4-methyl-piperazin-1-ylmethyl)-5H-imidazo[4,5-c]pyridine;

the compound is not 5-[5-(5-azabenzimidazolyl)methyl)-1-(4-cyanobenzyl)imidazole;

the compound is not 5-(5-benzyl-2,3-dihydro-benzofuran-2-ylmethyl)-5H-imidazo[4,5-c]pyridine;

the compound is not 5-[2-[4-(phenylmethyl) phenoxy]ethyl] -5H-imidazo[4,5-c]-pyridine hydrate;

the compound is not 5-[2-[4-(phenylmethoxy) phenoxy]ethyl]-5H-imidazo[4,5-c]-pyridine;

the compound is not 5-[2-[4-(phenoxyphenoxy)ethyl]-5H-imidazo[4,5-c]-pyridine;

the compound is not 5-[3-[4-(phenoxyphenoxy)propyl]-5H-imidazo[4,5-c]-pyridine;

the compound is not 5-[2-[4-(4-fluorophenoxy)phenoxy)ethyl]-5H-imidazo[4,5-c]-pyridine;

the compound is not 5-[3-[4(phenylmethyl)phenoxy)propyl]-5H-imidazo[4,5-c]-pyridine;

the compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[3-(5H-imidazo-[4,5-c]pyridin-5-yl)propyl]thio]-phenol hydrate;

the compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[2-(5H-imidazo-[4,5-c]pyridin-5-yl)ethyl]thio]-phenol hydrate;

the compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[4-(5H-imidazo-[4,5-c]pyridin-5-yl)buthyl]thio]-phenol hydrate;

the compound is not (±) 2,6-bis(1,1,-dimethylethyl)-4-[[2-hydroxy-3]-(5h-imidazo-[4,5-c]pyridin-5-yl)buthyl]thio]-phenol hydrate;

8. The compound according to claim 7, wherein:

R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6, heterocyclic ring unsubstituted or substituted with one or more R^6, C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6;

Y is selected from the group consisting of a single bond , O; $S(O)_m$; NR^{11}; and a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain, said heteroatoms being selected from the groups consisting of O, S, and N; such as C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}-$and C_{3-10} cycloalkylidene;

each R^2 and R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;

X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2$), $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as $-CH=CH-CH_2-$), C_{2-6} alkynylene;

-m is any integer from 0 to 2;

R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl-NR^{10}-; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;; and each of said aryl, aryloxy, arylthio, aryl-NR^{10}-, 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring is optionally substituted with one or more R^{17}; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

R^5 is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;

each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10}

cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19};

each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocyclic ring; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof; alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocyclic ring;

each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;

each R^{10} and R^{11} is independently selected from the group the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocyclin ring; an amino acid residue linked through a carboxyl group thereof;

R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through an amino group thereof;

each R^{13} and R^{14} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof;

each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through a carboxyl group thereof;

R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2; $NR^{20}R^{21}$; OCF_3; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6}$ alkyl), $N(H)S(O)(O)(C_{1-6}$ alkyl); aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring each

unsubstituted or substituted with 1 or more halogens;
each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;
R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl, ; C_{4-10} cycloalkenyl;
each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;
R^{25} and R^{26} are hydrogen.

9. The compound according to claim 7 or 8 wherein YR^1 is not hydrogen, an unsubstituted C_{3-10} cycloalkyl, or a C_{1-6} alkyl.

10. The compounds according to any one of claims 7 to 9, wherein Y R^1 is not phenyl para substituted with OH.

11. The compounds according to any of claims 7 to 10 wherein Y R^1 is fluorophenyl.

12. The compound according to any one of claims 7 to 10, wherein R^1 is a naphtenyl.

13. The compound according to any one of claims 7 to 12, wherein R^3 is selected from an aryl unsubstituted or substituted with 1-3R^6, wherein at least one R^6 is a halogen or a C_{1-6} alkyl

14. The compound according to claim 7, wherein either R^2 or R^4 is O and either R^{25} or R^{26} is cyclopentyl or cyclohexyl.

15. The compound according to claim 7, selected from the group consisting of:
2-(2,6-Difluorophenyl)-5-[(2,6-difluorophenyl)methyl]-5*H*-imidazo[4,5-c]pyridine
5-Benzyl-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(2,6-Difluorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-Benzyl-2-phenyl-5*H*-imidazo[4,5-c]pyridine
2-Phenyl-5-(3-phenylpropyl)-5*H*-imidazo[4,5-c]pyridine
5-[(2-Chlorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(3-Chlorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(4-Chlorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine

5-[(2-Methoxyphenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(3-Methoxyphenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(4-Methoxyphenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(4-Methylphenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(2-Fluorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(3-Fluorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(4-Fluorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(2-Methylphenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(3-Methylphenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
4-[(2-Phenyl-5*H*-imidazo[4,5-c]pyridin-5-yl)methyl]-benzonitrile
2-Phenyl-5-[[4-(trifluoromethyl)phenyl]methyl]-5*H*-imidazo[4,5-c]pyridine
5-[(4-Chlorophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine hydrochloride
5-[(5-Chloro-2-thienyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-(2-Naphthalenylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine
2-Phenyl-5-(4-phenylbutyl)-5*H*-imidazo[4,5-c]pyridine
5-([1,1'-Biphenyl]-4-ylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine
2-Phenyl-5-(1-phenylethyl)-5*H*-imidazo[4,5-c]pyridine
5-(1-Naphthalenylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine
2-(2,6-Difluorophenyl)-5-[(2,4-difluorophenyl)methyl]-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(2-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(2-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(3-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(4-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(2-pyridinyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(2-thienyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(1-naphthalenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(2-naphthalenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Iodophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(3-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(3-methylphenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(3-methoxyphenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Chlorophenyl)methyl]-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Chlorophenyl)methyl]-2-(3-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(2-Phenoxy-ethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine
5-(3-Phenyl-prop-2-en-1-yl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine
2-(3-Bromophenyl)-5-[(4-iodophenyl)methyl]-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-[(phenylthio)methyl]-5*H*-imidazo[4,5-c]pyridine
5-[(4-Bromophenyl)methyl]-2-[3-(trifluoromethyl)phenyl]-5*H*-imidazo[4,5-c]pyridine
5-([1,1'-Biphenyl]-4-ylmethyl)-2-(2-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine
5-[(4-Chlorophenyl)methyl]-2-(2-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine
2-(2-Fluorophenyl)-5-[(4-iodophenyl)methyl]-5*H*-imidazo[4,5-c]pyridine
5-[[4-(1,1-Dimethylethyl)phenyl]methyl]-2-(2-fluorophenyl)-5H-imidazo[4,5-c]pyridine

16. A composition for separate, combined or sequential use in the treatment or prophylaxis of anti-viral infections, comprising:

a) one or more compounds according to claim 7, and,

b) one or more compounds effective in the treatment or prophylaxis of viral infections, including Flaviviral or Picornaviral enzyme inhibitors,
in proportions such as to provide a synergistic effect in the said treatment of prophylaxis.

17. The composition according to claim 16, wherein said one or more compounds effective in the treatment or prophylaxis of viral infections are interferon alpha or ribavirin.

18. The use of the compounds of any one of claims 7 to 15 for the preparation of a medicament for the treatment of viral infections.

19. A method for preparing the compounds of claim 7 comprising essentially the steps of

a) reacting a (substituted) 3,4-diaminopyridine (A) is reacted with B (Y-R1) to give imidazo[4,5-c]pyridines (C);

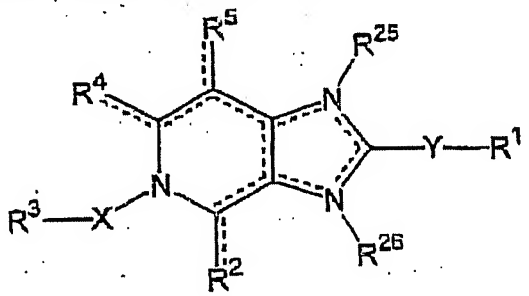
b) introducing further substituents (R^2, R^4 and/or $R^5 \neq H$) either a) by cylization of an appropiately substituted 3,4-diaminopyridine (A) or b)) by introduction of the substituent(s) onto the imidazo[4,5-c]pyridine (C);

c) reacting the imidazo[4,5-c]pyridines (C) with an alkylating agent (D) (R^3-X-R^6) in an appropiate solvent under addition of a base at ambient temperature;

optionally, in the case of hydroxy, mercapto or amino substituents in position 4 or 6 of the imidazopyridine I (Z = O, S or NR);

d) introduction of a further substituent (R^{25} or R^{26}) at position 1 or 3 of the imidazo[4,5-c]pyridine.

20. A method for preventing or treating a viral infections in a subject or patient by administering to the patient in need thereof a therapeutically effective amount of one or more imidazo[4,5-c]pyridine derivatives according to formula (Z):



(Z)

wherein:

- the dotted lines represent an optional double bond, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;
- R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6, heterocyclic ring unsubstituted or substituted with one or more R^6, C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6;
- Y is selected from the group consisting of a single bond , O; $S(O)_m$; NR^{11}; and a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain, said heteroatoms being selected from the groups consisting of O, S, and N; such as C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}-$and C_{3-10} cycloalkylidene;
- each R^2 and R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; or, when one of R^{25} or R^{26} is different from hydrogen, either R^2 or R^4 is selected from (=O), (=S), and ($=NR^{27}$);
- X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2$), $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as $-CH=CH-CH_2-$), C_{2-6} alkynylene;
- m is any integer from 0 to 2;
- R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl-NR^{10}-; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; and each of said aryl, aryloxy, arylthio, aryl-NR^{10}-, 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring is optionally substituted with one or more R^{17}; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond

cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

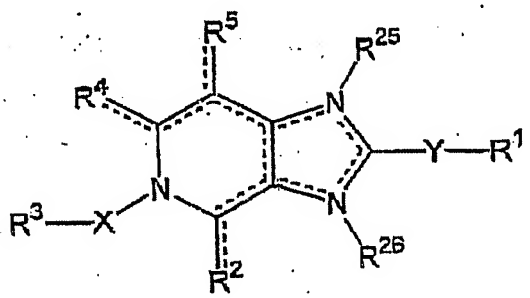
- R^5 is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;
- each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^{18}$; $C(=S)R^{18}$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19};
- each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocyclic ring; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof; alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocyclic ring;
- each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;
- each R^{10} and R^{11} is independently selected from the group the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocyclin ring; an amino acid residue linked through a carboxyl group thereof;
- R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through an amino group thereof;
- each R^{13} and R^{14} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof;

- each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through a carboxyl group thereof;
- R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2; $NR^{20}R^{21}$; OCF_3; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6}$ alkyl), $N(H)S(O)(O)(C_{1-6}$ alkyl); aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring each unsubstituted or substituted with 1 or more halogens;
- each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;
- R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl, ; C_{4-10} cycloalkenyl;
- each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;
- each R^{25} or R^{26} are absent or selected from the group consisting of of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; (C_{3-8} cycloalkyl)-C_{1-3} alkyl;; aryl, such as phenyl; 5 or 6 membered heterocyclic ring, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, (C_{3-8} cycloalkyl)-C_{1-3} alkyl, C_{5-10} bicycloalkyl, adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, oxybenzyl, and OH; and heterocyclic ring having 3 to 7 carbon atoms, preferably a saturated heterocyclic ring wherein the heteroatoms are S, S(O), or $S(O)_2$ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocyclic ring carbon atoms. Provided that either R^{25} or R^{26} is hydrogen. Typically R^{25} or R^{26} is cyclopentyl or cyclohexyl; provided that if the compound is substituted at R^{25} or R^{26}, either R^2 or R^4 is selected from (=O), (=S), and ($=NR^{27}$); and
- R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl; aryl; arylalkyl, such as benzyl;

as an active ingredient, optionally in a mixture with at least a pharmaceutically acceptable carrier.

21. A method of screening antiviral compounds which comprises

a) providing a compounds of the formula (Z)



(Z)

wherein:

- the dotted lines represent an optional double bond, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;
- R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6, heterocyclic ring unsubstituted or substituted with one or more R^6, C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6;
- Y is selected from the group consisting of a single bond , O; $S(O)_m$; NR^{11}; and a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain, said heteroatoms being selected from the groups consisting of O, S, and N; such as C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}-$and C_{3-10} cycloalkylidene;
- each R^2 and R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; or, when one of R^{25} or R^{26} is different from hydrogen, either R^2 or R^4 is selected from (=O), (=S), and ($=NR^{27}$);

- X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2$), $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as $-CH=CH-CH_2-$), C_{2-6} alkynylene;
- m is any integer from 0 to 2;
- R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl-NR^{10}-; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;; and each of said aryl, aryloxy, arylthio, aryl-NR^{10}-, 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring is optionally substituted with one or more R^{17}; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;
- R^5 is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring;
- each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2; NR^7R^8; OCF_3; haloalkyl; $C(=O)R^{18}$; $C(=S)R^{18}$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19};
- each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocyclic ring; $C(=O)R^{12}$; $C(=S)$ R^{12} ; an amino acid residue linked through a carboxyl group thereof;

alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocyclic ring;

- each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;
- each R^{10} and R^{11} is independently selected from the group the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocyclin ring; an amino acid residue linked through a carboxyl group thereof;
- R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through an amino group thereof;
- each R^{13} and R^{14} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof;
- each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through a carboxyl group thereof;
- R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2; $NR^{20}R^{21}$; OCF_3; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6}$ alkyl), $N(H)S(O)(O)(C_{1-6}$ alkyl); aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring each unsubstituted or substituted with 1 or more halogens;
- each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;
- R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl, ; C_{4-10} cycloalkenyl;
- Each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;

- each R^{25} or R^{26} are absent or selected from the group consisting of of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; (C_{3-8} cycloalkyl)-C_{1-3} alkyl;; aryl, such as phenyl; 5 or 6 membered heterocyclic ring, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, (C_{3-8} cycloalkyl)-C_{1-3} alkyl, C_{5-10} bicycloalkyl, adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, oxybenzyl, and OH; and heterocyclic ring having 3 to 7 carbon atoms, preferably a saturated heterocyclic ring wherein the heteroatoms are S, S(O), or $S(O)_2$ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocyclic ring carbon atoms. Provided that either R^{25} or R^{26} is hydrogen. Typically R^{25} or R^{26} is cyclopentyl or cyclohexyl; provided that if the compound is substituted at R^{25} or R^{26}, either R^2 or R^4 is selected from (=O), (=S), and (=NR^{27}); and
- R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl; aryl; arylalkyl, such as benzyl;

and

b) determining the anti-viral activity of said compound.

22. The method of claim 21, wherein said anti-viral activity is determined by the activity of said compound against one or more viruses belonging to the family of the Flaviviridae and/or of the Picornaviridae.

US Patents 4,914,108, 4,990,518, 4,988,707, 5,227,384, 5,302,601 and 5,486,525 describe 5-substituted [4,5-c]imidazopyridine derivatives useful in the treatment of diseases or disorders mediated by platelet-activating factor. The compounds were found to inhibit ^{3}H-PAF binding to human platelets.

EP 1132381 describes esters of 2,2-dimethylpropionic acid comprising a benzimidazole structure having an inhibitory activity of elastase.

WO 96/1192 describes compounds of the general formula Ar1-Q-Ar2-Y-R-Z, wherein Z is optionally a [4,5-c]imidazopyridine which are proposed as LTA4 hydrolase inhibitors useful for the treatment of inflammatory diseases mediated by LTB_4 production.

WO 96/12703 describes heteroarylthioalkyl thiophenolic compounds having 5-lipoxygenase inhibitory activity which are suggested to be useful in the treatment of 5-lipoxygenase mediated conditions.

Chemical Abstracts acc no. 1987:18435 and Chemical Abstracts acc no. 1983:594812 describe the synthesis of two imidazo[4,5-b] and of imidazo[4,5c]pyridine derivatives substituted with piperazinyl and furanyl groups.

EP 1162196 describes fused ring compounds for the use as therapeutic agents for hepatitis C. The fused 5 and 6 membered ring is made up of optionally subsituted carbon atoms or nitrogen atoms and optionally one oxygen, sulfur atom or substituted nitrogen atom on the 5 membered ring. WO 95/02597 describes imidazo[4,5c]pyridine derivatives not substituted at the N5 with antiviral activity

GB2158440 describes 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine derivatives with antiviral activities.

STN database accession 110:165603 & Khimiko-Farmatsevtichsskii Zurnal, 23:1, (1989), 26-59, describe spinacearnine derivatives such as 5H-imidazo [4,5-c]pyridine-5-ethanol, 1,4,6,7-tetrahydro-alpha-(4methoxyphenyl)-1,2-dimethyl compounds with antiviral activity (small pox virus).

STN database accession 132:222537 and HU78019 describe N-alkylated azoles with antibacterial activity.

WO9927929 describes [4.3.0] nitrogen containing ring systems and homologous compounds which are proposed as farnesyl-protein transferase inhibitors applicable in the treatment of cancer.

WO9611192 describes 5-substituted imidazo(4,5)pyridine compounds and related moleules for use as anti-imflammatory compounds by inhibiting leukotriene A4 hydrolase.

EP344414 describes 5-Substitued imidazo[4,5-c]pyridines for the treatment of diseases such as inflammation, cardiovascular disorders and asthma .

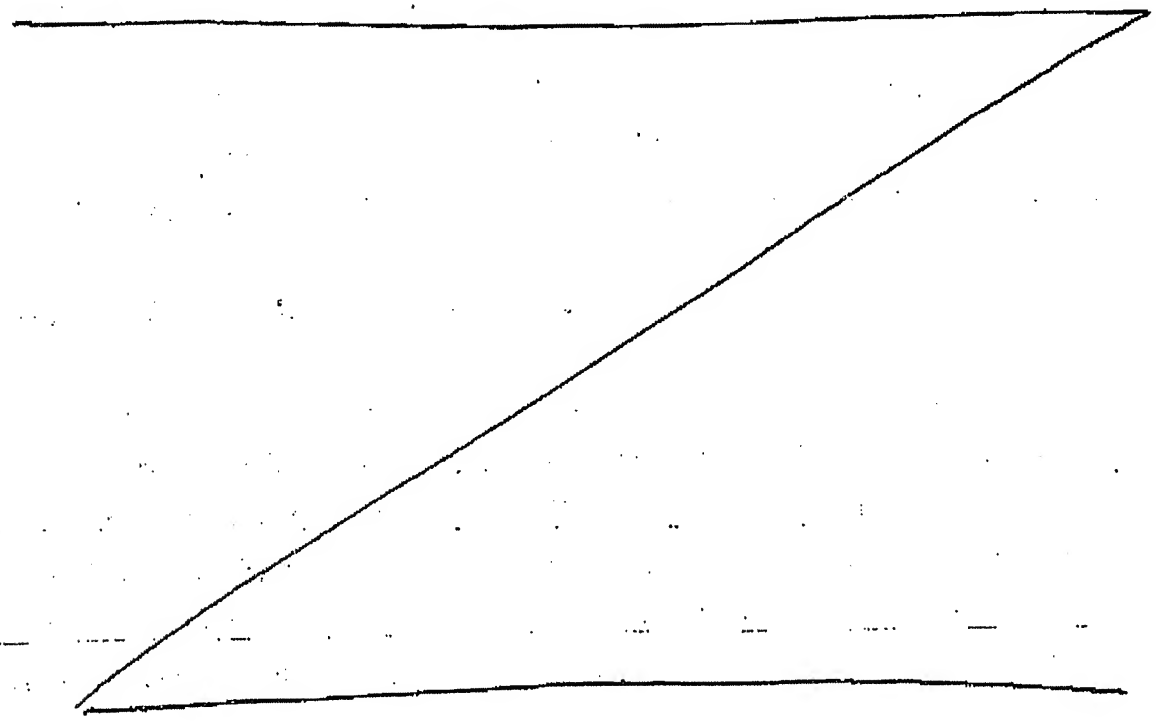
WO9516687 decribes imidazopyridine indoles which act as platelet activating factor antagonists:

J. Comb. Chem. (2002) 4:5, 475-483 describes the synthesis of benzimidazole compound for use in small organic libraries.

In view of their important pharmacological value, there is a need for drugs having antiviral activity, optionally selective activity against viruses belonging to the family of Flaviviridae including hepatitis C virus, and against viruses belonging to the family of Picornavidae.

SUMMARY OF THE INVENTION

In the present invention, new selective anti-viral compounds are being provided. The compounds are imidazo[4,5-c]pyridine derivatives and it has been shown that they possess a broad anti-viral activity. Members of the Flaviviridae and of the Picornaviridae families are being inhibited. The present invention demonstrates that the compounds inhibit the replication of BVDV, HCV and Coxsackie virus. Furthermore, the anti-BVDV activity of the compounds is based on the inhibition of the viral polymerase enzyme of BVDV. Therefore, these



- the compound is not not 5-(5-benzyl-2,3-dihydro-benzofuran-2-ylmethyl)-5H-imidazo[4,5-c]pyridine (as disclosed in WO96/11192);
- the compound is not 5-[2-[4-(phenylmethyl) phenoxy]ethyl] -5H-imidazo[4,5-c]-pyridine hydrate (as disclosed in WO96/11192);
- the compound is not 5-[2-[4-(phenylmethoxy) phenoxy]ethyl]-5H-imidazo[4,5-c]-pyridine (as disclosed in WO96/11192);
- the compound is not 5-[2-[4-(phenoxyphenoxy)ethyl]-5H-imidazo[4,5-c]-pyridine (as disclosed in WO96/11192);
- the compound is not 5-[3-[4-(phenoxyphenoxy)propyl]-5H-imidazo[4,5-c]-pyridine (as disclosed in WO96/11192);
- the compound is not 5-[2-[4-(4-fluorophenoxy)phenoxy)ethyl]-5H-imidazo[4,5-c]-pyridine (as disclosed in WO96/11192);
- the compound is not 5-[3-[4(phenylmethyl)phenoxy)propyl]-5H-imidazo[4,5-c]-pyridine (as disclosed in WO96/11192);
- The compound is not [5-(4-Fluorobenzyl)-5H-imidazo[4,5-c]pyridin-2-yl]-methylamine (X=CH_2, Y=NR11, wherein R11=methyl, R1=R^2=H, R^3=phenyl substituted with 1 R^{17} in para, wherein R^6 is F, R4=H, R5=H) (as disclosed in EP76530);
- The compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[3-(5H-imidazo-[4,5-c]pyridin-5-yl)propyl]thio]-phenol hydrate (X=CH_2-CH_2-CH_2, Y=bond; R1= hydrogen, R^2=H, R^3=thiophenyl substituted with 3 R^6, wherein R^6=2 branched C4 alkyl in meta and OH in para) (as disclosed in WO96/12703);
- The compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[2-(5H-imidazo-[4,5-c]pyridin-5-yl)ethyl]thio]-phenol hydrate (X=S-CH_2-CH_2, Y=bond; R1= hydrogen, R^2=H, R^3=thiophenyl substituted with 3 R^6, wherein R^6=2 branched C4 alkyl in meta and OH in para) (as disclosed in WO96/12703);
- The compound is not 2,6-bis(1,1,-dimethylethyl)-4-[[4-(5H-imidazo-[4,5-c]pyridin-5-yl)buthyl]thio]-phenol hydrate (X=S-CH_2-CH_2-CH_2, Y=bond; R1= hydrogen, R^2=H, R^3=thiophenyl substituted with 3 R^6, wherein R^6=2 branched C4 alkyl in meta and OH in para) (as disclosed in WO96/12703);
- The compound is not (±) 2,6-bis(1,1,-dimethylethyl)-4-[[2-hydroxy-3]-(5H-imidazo-[4,5-c]pyridin-5-yl)buthyl]thio]-phenol hydrate (X=S-CH_2-CHOH-CH_2, Y=bond; R1= hydrogen, R^2=H, R^3=thiophenyl substituted with 3 R^6, wherein R^6=2 branched C4 alkyl in meta and OH in para) (as disclosed in WO96/12703);

- The compound is not 5-[2-(4-Phenylmethyloxy-phenoxy)-ethyl]-5H-imidazo[4,5-c]pyridine (X=CH_2CH_2, Y=bond, R1=hydrogen, R^2=H, R^3=phenoxy substituted with 1 R^{17} in para, wherein R^{17} = benzyl oxy) (as disclosed in WO96/11192);
- The compound is not 5-[3-(4-Phenoxy-phenoxy)-propyl]-5H-imidazo[4,5-c]pyridine (X=$CH_2CH_2CH_2$, Y=bond, R1=hydrogen, R^2=H, R^3=phenoxy substituted with 1 R^6 in para, wherein R^6=phenoxy substituted in para with F; R4=H) (as disclosed in WO96/11192);
- The compound is not 5-{2-[4-(4-Fluorophenoxy)-phenoxy]-ethyl}-5H-imidazo[4,5-c]pyridine (X=CH_2CH_2, Y=bond, R1=hydrogen, R^2=H, R^3=phenoxy substituted with 1 R^6 in para, wherein R^6=phenoxy, substituted in para with F; R4=H) (as disclosed in WO96/11192);
- The compound is not 5-[3-(4-Phenylmethyl-phenoxy)-propyl]-5H-imidazo[4,5-c]pyridine (X=$CH_2CH_2CH_2$, Y=bond, R1=hydrogen, R^2=H, R^3=phenoxy substituted with 1 R^6 in para, wherein R^6=benzyl ;R4=H) (as disclosed in WO96/11192);
- The compound is not (1H-Indol-3-yl)-[3-(2-methyl-5H-imidazo[4,5-c]pyridine-5-carbonyl)-phenyl]-methanone (X=-(C=O)- or SO_2, Y= CH_2, R1=H, R^2=H, R^3= phenyl substituted with 1 R^6, wherein R^6 is C(=O) R^{18}, wherein R^{18} is indole) (as disclosed in US 5,486,525);
- the compound is not 4 or 3-[(2-methyl-5H-imidazo[4,5-c]pyridin-5-yl)methyl]-benzoic acid alkylester or 5-[4 or 3-(alkoxycarbonyl-phenyl)-methyl]-2-methyl-5H-imidazo[4,5-c]pyridine, in particular 4 or 3-[(2-methyl-5H-imidazo[4,5-c]pyridin-5-yl)methyl]-methyl ester (X=CH_2, Y=CH_2, R1=H, R^2=H, R^3=phenyl substituted at the para or meta position with 1R^{17}, wherein R^{17} is (C=O)R^{18}, wherein R^{18}=alkoxy) (as disclosed in US 5,486,525)
- the compound is not 5-[(fluorophenyl)methyl]-2-amino-5-H-imidazo[4,5-c]-pyridine (XR^3 = fluorobenzyl, Y=NR^{11} with R^{11}=methyl, R^1=H, R^2, R^3, R^4=H) (as disclosed in US 5,137,896);
-

- the compound is not ((5-[4-(Fluorophenyl)methyl]-5-H-imidazo[4,5-c]-pyridine-2-yl) methyl)-carbamaat, methyl ester (XR^3 = fluorobenzyl, Y = C(=O)R12 with R12 = methyl, R^1 = H, R^2, R^3, R^4 = H) (as disclosed in US 5,137,896);
- the compound is not 5-(4-Chlorophenylmethyl)-2-(piperidin-1-ylmethyl)-5H-imidazo[4,5-c]pyridine and its dihydrochloride salt (XR^3 = chlorobenzyl, Y = -CH_2-, R^1 = piperidinyl) (as disclosed in Justus Liebigs Annalen der Chemie (1971), 747, 158-171);
- the compound is not 5-(4-Chlorophenylmethyl)-2-(4-methyl-piperazin-1-ylmethyl)-5H-imidazo[4,5-c]pyridine (XR^3 = chlorobenzyl, Y = -CH_2-, R^1 = piperazinyl, R^6 = methyl) (as disclosed in Journal of the Chemical Society [section B]: Physical Organic (1966), 4, 285-291);
- the compound is not 5-[5-(5-azabenzimidazolyl)methyl)-1-(4-cyanobenzyl)imidazole (as disclosed in WO99/27929);

Particularly, the invention relates to a compound according to the general formula (Z) and/or A as described above wherein,

- if Y is a bond and R^1 is an aryl, this aryl is not phenyl para substituted with OH and optionally further substituted with methyl, methoxy, nitro, diethylamino, Cl, Br, or F ; or, if Y is a bond and R1 is an aryl para substituted with OH and optionally further substituted with methyl, methoxy, nitro, diethylamino, Cl, Br, or F, and X is an alkylene, R^3 is not a heterocyclic ring containing N;
  and/or
- if Y is a bond or $(CH_2)_{1-6}$, R^1 is H, X is CH_2 and R^3 is phenyl with $1R^{17}$, wherein R^{17} is $C(=O)R^{18}$, then R^{18} is selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof; i.e. R18 is not a C_{3-10} cycloalkyl or C_{4-10} cycloalkenyl;
  and/or
- if Y is a bond or $(CH2)_{1-6}$, then R^1 is an aryl unsubstituted or substituted with one or more R^6, heterocyclic ring unsubstituted or substituted with one or more R^6, C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6 ; i.e. YR1 is not H or C_{1-6} alkyl;
  and/or
- if Y is a bond or $(CH2)_{1-6}$, R^1 is H, and R^3 is a 5 membered heterocyclic ring with one R^{17}, wherein R17 is C(=O)R18 and R18 is $NR^{15}R^{16}$, then R^{15} and R^{16} are not a C_{1-18} alkyl or a cycloalkyl; or

if Y is a bond or $(CH2)_{1-6}$, and R^1 is H, and R^3 is a 5 membered heterocyclic ring with one R^{17}, wherein R17 is C(=O)R18 then R18 is selected from H; OH; C_{1-18} alkyl; C_{2-18}

cycloalkynyl; 5 or 6 membered heterocyclic, oxyheterocyclic or thioheterocyclic ring; i.e., R^5 is not an aryl, aryloxy or benzyl;

The compounds of the invention optionally exclude those compounds according to the general formula (Z) and/or (A) as described above, wherein YR^1 is not hydrogen, an unsubstituted C_{3-10} cycloalkyl, or a C_{1-6} alkyl.

The compounds of the invention optionally exclude those compounds according to the general formula (Z) and/or (A) as described above, wherein Y R^1 is not phenyl para substituted with OH.

The compounds of the invention optionally exclude those compounds according to the general formula (Z) and/or (A) as described above, wherein R^1 is not H, Y is not NR^{11} with R11 C_{1-6} alkyl or methyl, and/or YR^1 is not monomethylamino.

The compounds of the invention optionally exclude those compounds according to the general formula (Z) and/or (A) as described above, wherein R^1 is a phenyl substituted with 1R6, R6 is $C(=O)R^{18}$ and R^{18} is t-butoxy.

The compounds of the invention optionally exclude those compounds according to the general formula (Z) and/or (A) as described above, wherein R^1 is not piperidinyl and is not piperazinyl subsituted with methyl.

The compounds of this invention optionally exclude those in which XR^3 is equivalent to the substructure $-(CH_2)n\text{-}Y'\text{-}C(O)\text{-}N(R_1')(R_2')$ set forth on column 1, line 49 to column 2 line 38 of US patent 5,302,601 wherein R_1' and R_2' are each independently selected from hydrogen; straight or branched chain alkyl of 1 to 15 carbon atoms; cycloalkyl having 3 to 8 carbon atoms; substituted cycloalkyl which can be substituted one or more by alkyl of 1 to 6 carbon atoms; bicycloalkyl having 3 to 8 carbon atoms in each ring; heterocyclicalkyl having 4 to 8 carbon atoms which can be optionally substituted by alkyl of 1 to 6 carbon atoms; heteroaromatic having 5 or 6 carbon atoms which can be optionally substituted by alkyl having 1 to 6 carbon atoms; phenyl; substituted phenyl which can be substituted one or more by a group independently selected from alkyl having 1 to 6 carbon atoms or halogen; straight or branched alkenyl having 3 to 15 carbon atoms with the proviso that the double bond of the

alkenyl group cannot be adjacent to the nitrogen; cycloalkenyl having 5 to 8 carbon atoms with the proviso that the double bond cannot be adjacent to the nitrogen; and R_1' and R_2' cannot both be hydrogen; Y' is phenyl or phenyl substituted once or more than at one or more of the 2, 3, 5 or 6 positions of the phenyl ring by substituents independently selected from the group consisting of alkoxy having 1 to 6 carbon atoms; halogen wherein the halogen is selected from bromo, fluoro, or chloro; straight or branched chain alkyl having 1 to 6 carbon atoms; substituted straight or branched chain alkyl which can be substituted one or more by halogen; thioalkyl wherein the alkyl has 1 to 6 carbon atoms; alkoxyalkyl wherein the alkyl groups are each 1 to 6 carbon atoms; hydroxyalkyl wherein the alkyl has 1 to 6 carbon atoms; alkylthioalkyl wherein the alkyl groups are each 1 to 6 carbon atoms; cyano; mercaptoalkyl wherein the alkyl has 1 to 6 carbon atoms; hydroxy; amino; alkylamino wherein the alkyl group has 1 to 6 carbon atoms; and dialkylamino wherein the alkyl groups are each 1 to 6 carbon atoms; n is an integer of 1 to 5 and the comparable disclosure in any member of the patent family of US patent 5,302,601, which disclosure is herewith expressly incorporated by reference.

The compounds of this invention optionally exclude those in which R^5 contains any of the substituents designated as « Ar » in WO 00/39127 (incorporated expressly herein by reference), in particular aryl, aryl phenoxy, or benzyl.

Typically, the compounds of this invention do not include the compounds of example 35 of US patent 5,302,601, example 6 of US Patent 4,990,518, examples 1 to 5 of US 4,988,707,

examples 3 and/or 11 of WO 96/12703 and/or compounds 340A, 347C, 349C, 351C, 355C and/or 356 C of WO 96/11192 and/or their methylene homologues, the disclosure of which are herewith expressly incorporated by reference.

Optionally, the compounds of this invention also exclude all methylene homologues of known compounds which are excluded from the scope of this invention.

The compounds of this invention optionally exclude those in which XR3 is equivalent to the substructure –(CH2)n-Het-C(O)-N(R1)(R2) set forth on column 1, line 41 to column 2 line 24 of US patent 4,990,518 and the comparable disclosure in any member of the patent family of US patent 4,990,518, which disclosure is herewith expressly incorporated by reference.

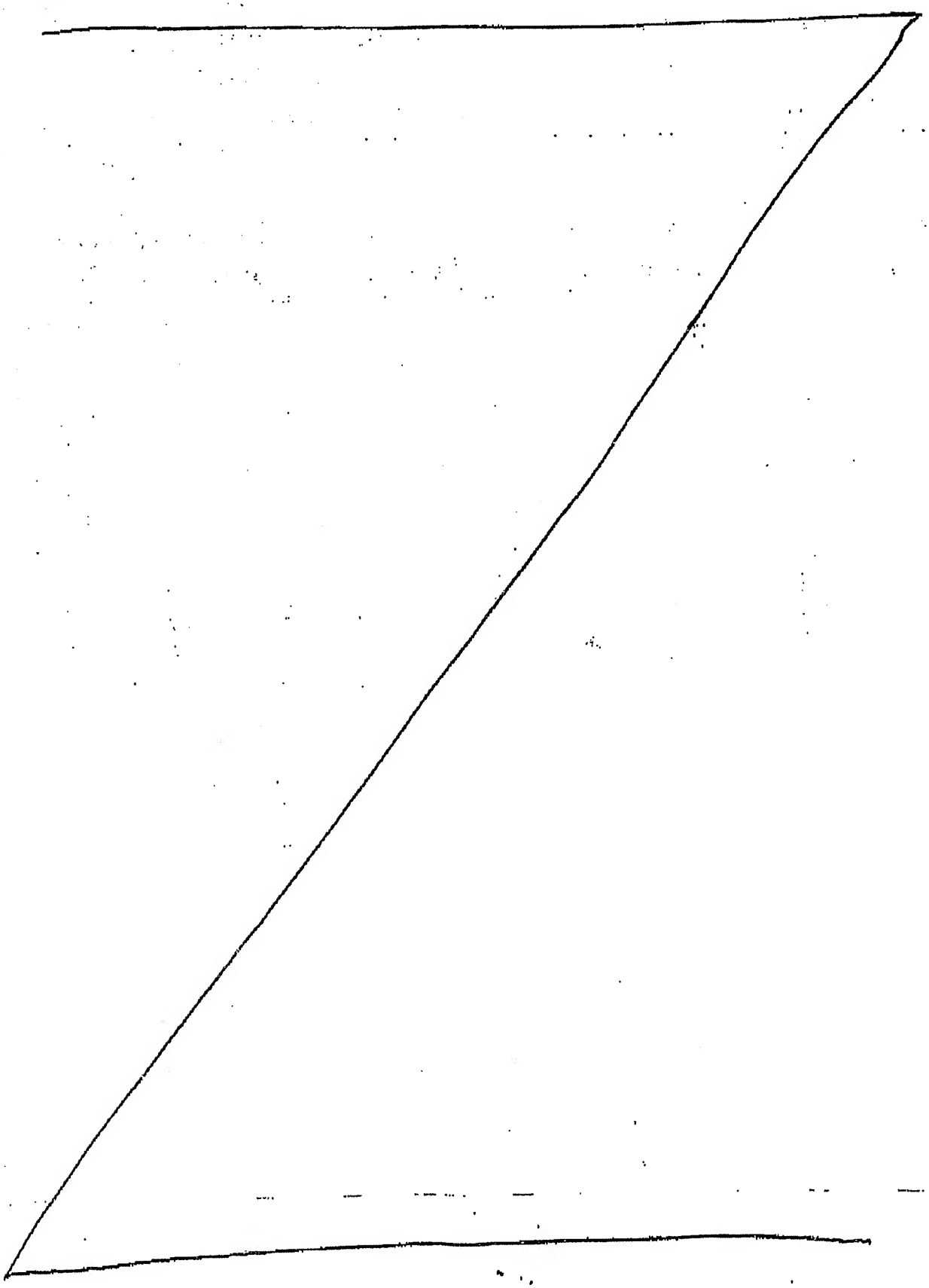
Typically the compounds of this invention do not include the compounds expressly disclosed in EP 76530, EP 1 162 196, EP 1132 381, US 5,486,525, US 5,137,896, US 5,227,384, US 4914108, US 5,302,601, US 5,208,242, US 4,990,518, US 4,988,707, DE 4211474, DE 4230464, WO 00/39127, WO 00/40586, WO 00/40583, WO 00/39127, WO 00/20416, WO99/27929, GB2158440, WO6111192, EP3444414, WO9516687, Chemical Abstracts acc no.110:165603, Chemical Abstracts acc no. 132:222537 -and any family member thereof in Chemical Abstracts acc no. 1987:18435 and Chemical Abstracts acc no. 1983:594812 and overlap with the compounds described in the present description, the disclosure of which is herewith expressly incorporated by reference.

Typically the compounds of this invention do not include the compounds expressly disclosed in EP 76530, EP 1 162 196, EP 1132 381, US 5,486,525, US 5,137,896, US 5,227,384, US 4914108, WO 00/39127, WO 00/40586, WO99/27929, GB2158440, WO6111192, EP3444414, WO9516687, Chemical Abstracts acc no. 1987:18435, Chemical Abstracts acc no.110:165603, Chemical Abstracts acc no. 132:222537 and Chemical Abstracts acc no. 1983:594812 and over which the claims of this application are not novel or do not posses an inventive step; the disclosure of these compounds is herewith expressly incorporated by reference.

Typically the compounds of this invention do not include the compounds expressly disclosed in Justus Liebigs Annalen der Chemie (1971), 747, 158-171 or in the Journal of the Chemical Society [section B]: Physical Organic (1966), 4, 285-291 and over which the claims of this

18 B

application are not novel or do not posses an inventive step; the disclosure of these compounds is herewith expressly incorporated by reference.



ственно не изменило величину светопропускания (0,25 усл. ед.), но увеличило коллоидно-осмотическое давление до 330 мм вод. ст. При этом время переживания сердца на эмульсии ПФОС, в составе которой находился 3 % полимер ОЭК (№ 3), достоверно возросло по сравнению с 2,5 % (ОЭК № 3) и составило в среднем 11,9 ч ($p<0,05$) (см. табл. 2).

Из полученных результатов видно, что из всех рассмотренных онкотических агентов в составе эмульсии ПФОС оптимальными свойствами для перфузии сердца обладают ОЭК с низкой молекулярной массой (80—100 кДа), с невысокой характеристической вязкостью (0,142—0,149 дл/г), хорошо совместимые с эмульсией ПФОС и создающие необходимое коллодно-осмотическое давление.

По-видимому, это объясняется тем, что если высокомолекулярный ОЭК с $\overline{M}_w$=200—450 кДа, применяемый обычно для плазмозамещения, попадая в русло крови, расщепляется амилолитическими ферментами до $\overline{M}_w$==40—70 кДа, обеспечивая необходимое коллоидно-осмотическое давление и необходимое время циркуляции в русле крови [2], то при перфузии сердца, где амилолитические ферменты отсутствуют, следует применять низкомолекулярный ОЭК, что хорошо согласуется с результатами эксперимента.

Таким образом, препараты на основе ОЭК могут быть использованы в целях консервации органов, где поддержание на физиологическом уровне коллоидно-осмотического давления является фактором, препятствующим развитию отека и удлиняющим сроки консервации.

SUMMARY

For cardiac perfusion, the most adequate oncotic agent was found to be oxyethyl starch having low molecular weight, low characteristic viscosity and inducing colloid-osmotic pressure close to the normal plasma protein levels.

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СИНТЕЗ И ПРОТИВОВИРУСНАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ СПИНАЦЕАМИНА

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Спинацеамин или 4,5,6,7-тетрагидроимидазо[4,5-с]пиридин содержится в секретах некоторых видов земноводных и, обладая бактериостатическими свойствами, защищает поверхность кожи данных животных [10—12]. Замещенные спинацеамины, как недавно было показано, способны проявлять высокую противовирусную активность и могут быть использованы в качестве лекарственных средств [13].

С целью развития исследований в данном направлении мы изучили противовирусную активность новых производных спинацеамина и их предшественников (IIв, IVг-з, Va, б, г, д), а также ранее описанных нами соединений этого ряда (IIа, б, IIIа, б, IVа-в, Vв) [2—9].

При взаимодействии 1-замещенных и 1,2-дизамещенных имидазо[4,5-с]пиридинов (Iа-е) с алкилгалогенидами и α-бромкетонами получены моночетвертичные и ацилметильные соли имидазо[4,5-с]пиридинов (IIа-в, IVа-з), которые затем восстанавливали $NaBH_4$ в спиртовой среде до соответствующих спинацеаминов (IIIа, б, Va-д).

Как мы и ожидали, в УФ-спектрах полученных спинацеаминов наблюдается одна коротковолновая полоса поглощения (207—208 нм), характерная

(2)

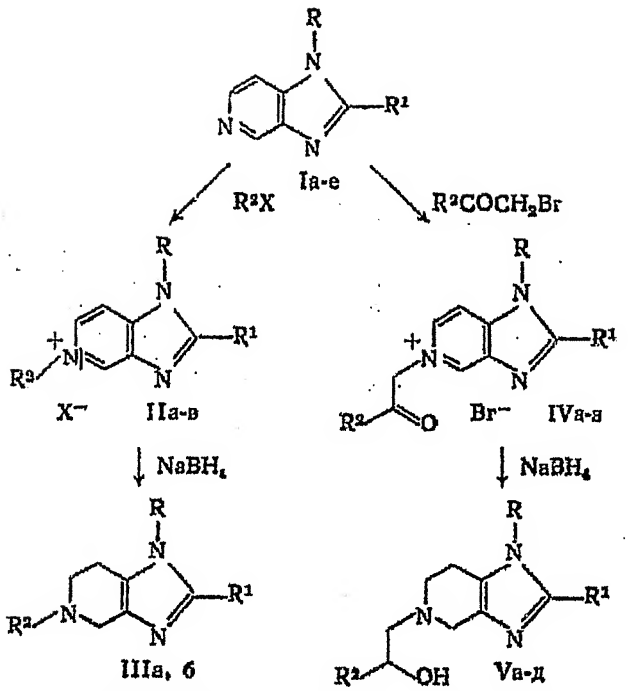
R^2

R^3

R = Me (Iа, б, г-е; IIа, IIIа, б; IVа-в; Vг), M (Iг; IVе), C_6H_3(C нафтил-2 (IVа), C

для имидазола. В т ные соли, кроме кор ют и длинноволнов 260 нм). В ИК-спе ных солей IVа-э, сня масле, имеется пол поглощения (1670— как в спектрах сп она отсутствует.

Строение спинаце и строение исходных лей IVд, ж подтве ПМР-спектров. Нап соли IVж (CF_3COO ся три синглета [3,09 (3-CH_3), 4,01 (OCH_3)]; синг группы фенацильн (6,51); два дублета (7,07 и 8,04); сигна ных протонов гетеро [H(5) и H(6)] и си C(4)-атоме. В элект данной соли спинаце сигналов протонов системы [при C(4,6,7 них появляются си ских протонов в обла



R = Me (Ia, б, г-е; IIa-в; IIIa, б; IVa-в, д-з; Va-д), CH_2Ph (Iв; IVг); R^1 = H (Iа; IIа, б; IIIа, б; IVа-в; Vг), Me (Iв, д; IVг; Va), SMe (Iб; IIв; IVд,ж, з; Vб,д), $SCH_2COC_6H_4Me$-4 (Iг; IVе), $C_6H_3(OMe)_2$-3,4 (Iе; Vв); R^2 = Me (IIа, в; IIIб), CH_2CH_2OH(IIб; IIIа), нафтил-2 (IVа), C_6H_4OMe-4 (IVб, е, ж; Va, в, д), Ph (IVв-д; Vб), Ad-2 (IVз; Vг); X = I (IIа, в), Cl (IIб).

для имидазола. В то же время исходные соли, кроме коротковолновой, имеют и длинноволновую полосу (250—260 нм). В ИК-спектрах ацилметильных солей IVа-з, снятых в вазелиновом масле, имеется полоса карбонильного поглощения (1670—1710 $см^{-1}$), тогда как в спектрах спинацеаминов Va-д она отсутствует.

Строение спинацеаминов Vб, д, как и строение исходных фенацилиевых солей IVд, ж подтверждено данными ПМР-спектров. Например, в спектре соли IVж (CF_3COOH, δ, м. д.) имеются три синглета метильных групп [3,09 (3-CH_3), 3,88 (NCH_3) и 4,01 (OCH_3)]; синглет метиленовой группы фенацильного заместителя (6,51); два дублета фенильного ядра (7,07 и 8,04); сигналы двух вицинальных протонов гетероциклического ядра [H(5) и H(6)] и синглет протона при C(4)-атоме. В спектре полученного из данной соли спинацеамина Vв уже нет сигналов протонов гетероциклической системы [при C(4,6,7)-атомах]. Вместо них появляются сигналы алифатических протонов в области сильного поля [4,63 м. д., CH_2 (4); 2,76 м. д., CH_2 (6); 2,5 м. д., CH_2 (7)].

Экспериментальная химическая часть

УФ-спектры соединений получены на спектрофотометре «Spectromom-204» (Венгрия) в воде, ИК-спектры записаны на спектрофотометре UR-20 (ГДР) в вазелиновом масле, спектры ПМР зарегистрированы на спектро-

Таблица 1

Производные имидазо[4,5-с]пиридина

Соединение	Выход, %	Т. пл., °С (растворитель для перекристаллизации)	Брутто-формула
IVг	81	244—5 (MeOH)	$C_{23}H_{23}BrN_2O$
IVд	85	209—11 (спирт)	$C_{16}H_{18}BrN_3OS$
IVе	74	155—7 (спирт)	$C_{21}H_{24}BrN_3O_3S$
IVж	73	216—7 (спирт)	$C_{17}H_{18}BrN_3O_2S$
IVз	81	213—4 (*i*-PrOH)	$C_{25}H_{28}BrN_3OS$
Va	97	206—7 (*i*-PrOH)	$C_{17}H_{24}Cl_2N_2O_2$
Vб	93	144—6 (*i*-PrOH)	$C_{16}H_{21}N_3OS$
Vг	73	184—5 (октан)	$C_{23}H_{23}N_2O$
Vд	66	124—6 (*i*-PrOH)	$C_{17}H_{23}N_3O_2S$

метре «Tesla» (60 МГц; ЧССР), в CF_3COOH с внутренним стандартом ТМС. Найденные величины элементных анализов соответствуют вычисленным.

2-Метилтио-1,5-диметил - 1Н-имидазо[4,5-с]пиридинийиодид (IIв). Смесь 2 г (10 ммолей) 1-метил-2-метилтиоимидазо[4,5-с]пиридина (Iб) и 1,5 г (12 ммолей) MeI в 10 мл спирта кипятят с обратным холодильником в течение 2 ч. Избыток MeI и спирта отгоняют в вакууме водоструйного насоса, полученную соль кристаллизуют из спирта. Выход IIв 89 %. Т. пл. 220—222 °С.

Ацилметильные соли (IVа-з). Растворяют 10 ммолей 1-замещенного или 1,2-дизамещенного имидазо[4,5-с]пиридина (Iа-е) в 50 мл ацетона и смешивают с 12 ммолями соответствующего α-бромкетона, растворенного в 20 мл ацетона. Смесь выдерживают при комнатной температуре в течение 4—6 ч и выделившуюся соль фильтруют, промывают ацетоном, эфиром, перекристаллизовывают из спиртов (табл. 1).

Спинацеамины Va-д. К раствору 10 ммолей ацилметильной соли 1-замещенного или 1,2-дизамещенного имидазо[4,5-с]пиридина в 200 мл воды и 200 мл MeOH прибавляют частями при перемешивании в течение 2 ч 60 ммолей $NaBH_4$. Затем реакционную массу выдерживают в течение 2 ч при 60—70 °С. Растворитель отгоняют в вакууме водоструйного насоса до объема 20—25 мл, выделившееся затвердевшее масло отфильтровывают, промывают водой и перекристаллизовывают из подходящего растворителя (см. табл. 1).

Соединения IIа, б получены кватернизацией основания Iа йодистым метилом и этиленхлоргидрином [6, 8]. Восстановление солей IIа, б до IIIа, б проводили $NaBH_4$ в спиртовой среде [3, 7]. Синтез соединений VIа-в и Vв описан ранее [4, 5, 9].

Экспериментальная биологическая часть

Противовирусные свойства соединений определяли в экспериментах на тканевых культурах в отношении вирусов: герпеса простого I типа (ВГП), осповакцины (ВОВ), классической чумы птиц (ВКЧП), болезни Ньюкасла (ВБН), везикулярного стоматита (ВВС), венесуэльского энцефаломиелита лошадей (ВВЭЛ), ЕСНО-6 методами скрининг-теста, редукции бляшек под агаровым покрытием, а также при введении веществ в состав поддерживающей среды [1]. С вирусом ЕСНО-6 исследования выполняли на монослойных культурах пассируемых кожно-мышечных клеток эмбриона человека, с остальными вирусами — на первично-трипсинизированных фибробластах эмбрионов кур.

Синтезированные вещества были в основном малотоксичны для тканевых культур, за исключением соединения IVе. Противовирусные свойства обнаружены почти у четверти исследованных соединений, при этом вещества с наиболее значимой активностью (IVб, е; Vб, д) выявлены в основном в экспериментах с вирусом осповакцины (табл. 2). Значительный интерес представляет соединение IVв, проявившее

Таблица 2

Характеристика противовирусного действия производных имидазо[4,5-с]пиридинов

Соединение	Вирус	Диаметр (в мм) зон при исследовании методом первичного просеивания: токсичности	Диаметр (в мм) зон при исследовании методом первичного просеивания: подавления образования бляшек	Тест редукции бляшек: исследованная концентрация, мкг/мл	Тест редукции бляшек: титр вируса, lg БОЕ/мл	Тест редукции бляшек: ХТИ
IIв	ВОВ	0	21	100*	2,12	1
				50	3,36	
				25	3,61	
				12	5,90	
				0	5,85	
	ECHO-6	0	23	100	3,5	2
				50	4,5	
				25	6,5	
				12	6,5	
				0	6,5	
IVб	ВОВ	12	11	12	2,12	4
				6	2,12	
				3	2,12	
				1,5	3,75	
				0	3,85	
IVв	ВКЧП	0	20	100	4,0	4
				50	4,0	
				25	4,0	
				12	4,66	
				0	5,36	
	ECHO-6	0	26	100	3,0	4
				50	3,0	
				25	5,0	
				12	6,5	
				0	6,5	
IVг	ВОВ	11	16	50	2,12	2
				25	2,12	
				12	3,61	
				6	3,75	
				0	3,85	
IVд	ВКЧП	0	30	50	4,0	2
				25	4,32	
				12	4,6	
				0	5,36	
IVе	ВОВ	10	24	3,0	2,12	8
				1,5	2,12	
				0,7	2,12	
				0,3	2,12	
				0,15	3,7	
IVж	ВОВ	30	10	25	2,12	1
				12	3,38	
				6	3,85	
				3	3,81	
				0	3,85	
Va	ВОВ	18	12	25	3,0	1
				12	3,99	
				6	4,39	
				3	4,53	
				0	4,57	
	ВВС	16	18	25	6,0	1
				12	7,04	
				6	7,32	
				3	7,47	
				0	7,56	
Vб	ВОВ	0	14	100	3,0	4
				50	3,0	
				25	3,0	
				12	4,46	
				0	4,57	
Vд	ВОВ	10	14	400	2,12	4
				200	2,12	
				100	2,12	
				50	3,35	
				0	3,85	
	ВКЧП	26	24	400	4,35	1
				200	5,11	
				100	5,27	
				50	5,02	
				0	5,36	

* Максимальная переносимая концентрация.

активность в отношени
сической чумы птиц и

SUMMARY

A series of novel deriva
ly occurring compound sy
tained by using quaterna
4,5-c/pyridine. Their antivi
ted.

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◆ УДК 615.31:547.831].0

*С. В. Шинкоренко, Е.
М. П. Перепичка, Н. Д*

**КИСЛОТНО-ОСНОВНЫЕ Х
ДИНИТРОФЕНИЛГИДРАЗО
И ИХ БИОЛОГИЧЕСКАЯ АК**

Черновицкий университет,
им. Н. И. Мечникова

Взаимодействием 1-
евых солей с диазоами
ли синтезированы и о
фенилгидразоны 1-ар
хинолиния различного
образной и ковалентно
же изучены их физио
ства [3, 8, 9]. Арилги
группой в гидразонно
чены конденсацией
вых солей с *п*-нитроф
том натрия. Показано
разоны обладают кис
и сольватохромными
10, 12].

Целью данной рабо
тез, изучение оптичес
новных и биологическ
гидразонов с двумя н
производных галоида
диния и лепидиния.

В работе приведен
о биологических свой

Таблица 2

...тивовирусного действия ...дазо [4,5-с] пиридинов

...аметр мм) зон ...исследо- ...ик мето- ...первич- ...просев- ...вания	Тест редукции бляшек		
	исследованная концентрация, мкг/мл	титр вируса, lg БОЕ/мл	ХТИ
21	100*	2,12	1
	50	3,36	
	25	3,61	
	12	3,90	
	0	3,86	
23	100	3,5	2
	50	4,5	
	25	6,5	
	12	6,5	
	0	6,5	
11	12	2,12	4
	6	2,12	
	3	2,12	
	1,5	3,75	
	0	3,85	
20	100	4,0	4
	50	4,0	
	25	4,0	
	12	4,66	
	0	5,36	
26	100	3,0	4
	50	3,0	
	25	5,0	
	12	6,5	
	0	6,5	
16	50	2,12	2
	25	2,12	
	12	3,61	
	6	3,75	
	0	3,85	
20	50	4,0	2
	25	4,32	
	12	4,6	
	0	5,36	
24	3,0	2,12	8
	1,5	2,12	
	0,7	2,12	
	0,3	3,12	
	0,15	3,7	
10	25	2,12	1
	12	3,38	
	6	3,85	
	3	3,81	
	0	3,85	
12	25	3,0	1
	12	3,99	
	6	4,39	
	3	4,53	
	0	4,57	
18	25	6,0	1
	12	7,04	
	6	7,32	
	3	7,47	
	0	7,56	
14	100	3,0	4
	50	3,0	
	25	3,0	
	12	4,46	
	0	4,57	
14	400	2,12	4
	200	2,12	
	100	2,12	
	50	3,35	
	0	3,85	
24	400	4,35	1
	200	5,11	
	100	5,37	
	50	5,02	
	0	5,36	

*носимая концентрация.

активность в отношении вирусов классической чумы птиц и ECHO-6.

SUMMARY

A series of novel derivatives of the naturally occurring compound spinaceamine were obtained by using quaternary salts of imidazo/4,5-c/pyridine. Their antiviral activity was tested.

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КИСЛОТНО-ОСНОВНЫЕ ХАРАКТЕРИСТИКИ МОНО- И ДИНИТРОФЕНИЛГИДРАЗОНОВ 2[4]-ФОРМИЛХИНОЛИНИЯ И ИХ БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ

Черновицкий университет, Харьковский НИИ микробиологии, вакцин и сывороток им. И. И. Мечникова

Взаимодействием 1-арилхинальдиниевых солей с диазоаминобензолами были синтезированы и охарактеризованы фенилгидразоны 1-арил-2(4)-формилхинолиния различного строения в солеобразной и ковалентной формах, а также изучены их физиологические свойства [3, 8, 9]. Арилгидразоны с нитрогруппой в гидразонном остатке получены конденсацией 1-арилхинальдиевых солей с *n*-нитрофенилантидиазотатом натрия. Показано, что такие гидразоны обладают кислотно-основными и сольватохромными свойствами [6, 10, 12].

Целью данной работы является синтез, изучение оптических, кислотно-основных и биологических свойств арилгидразонов с двумя нитрогруппами — производных галондарилатов хинальдиния и лепидиния.

В работе приведены также данные о биологических свойствах арилгидразонов с одной нитрогруппой в гидразонном остатке.

Для получения динитрофенилгидразонов 2(4)-формилхинолиния использовали конденсацию 2,4-динитрофенилгидразина с солями 2(4)-формил-1-арилхинолиния. Эти альдегиды получали кислотным гидролизом соответствующих азометинов [5] и использовали без выделения из реакционной массы.

Динитрофенилгидразоны, полученные в солеобразной форме (А) в виде желто-коричневых кристаллических продуктов, хорошо растворимы в ДМФА, слабо — в ацетоне, спиртах, плохо — в диоксане, хлороформе (табл. 1). В щелочном растворе происходит отщепление аниона, и гидразоны А приобретают строение диазометиндигидрохинолинов (В), которые не выделялись. Этот процесс сопровождается углублением окраски от желтой до сине-фиолетовой и смещени-

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 691.P2F	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2007/015553	International filing date *(day/month/year)* 06 July 2007 (06.07.2007)	Priority date *(day/month/year)* 07 July 2006 (07.07.2006)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GILEAD SCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

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	Date of issuance of this report 13 January 2009 (13.01.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/015553	06.07.2007	07.07.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D403/14 A61K31/4353 A61P31/12

Applicant
GILEAD SCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	BOURGHIDA, E Telephone No. +31 70 340-9517

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/015553

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 16-21 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 16-21 (with respect to industrial applicability) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15,22-27
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 Claims 16-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2.1 Reference is made to the following documents:

D1: WO 2005/063744 A (LEUVEN K U RES & DEV [BE]; PUERSTINGER GERHARD [AT]; GILEAD SCIENCES I) 14 July 2005 (2005-07-14)

D2: WO 2004/072243 A (ENANTA PHARMACEUTICALS INC [US]; MIAO ZENWEI [US]; SUN YING [US]; WU F) 26 August 2004 (2004-08-26)

Methods of treatment:

3.1 Claims 16-21 relate to subject-matter considered by this Authority to be coveredby the provisions of Rule 39.1(iv)/67.1(iv) PCT.

3.2 The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty:

4.1 D1 discloses the compound 5H-imidazo[4,5-c]pyridine, 5-[[6-(2,4-difluorophenyl)-3-pyridazinyl]methyl]-2-(2-fluorophenyl) used to treat HCV (see D1: example 317 page 189; description page 1).

4.2 The compound of claim 5 differs from the example of D1 in that it possesses trifluoromethyl groups in position 2 and 4 of the phenyl ring attached to pyridazine ring, whereas in the example of D1 the said phenyl ring is substituted by fluor atoms at the said positions.

4.3 D2 discloses the compound 3(2H)-pyridazinone, 5-paramethoxyphenyl-5-((2-cyclopropylaminothiazol-4-yl)) used as synthetic intermediate (see D2: compound 186h page 220).

4.4 The compounds of claims 27 differ from the example of D2 in that they possess trifluoromethyl groups in position 2 and 4 of the phenyl ring attached to pyridazine ring, whereas in the example of D1 the said phenyl ring is substituted by a methoxy group at the position 4.

4.5 Thus, the subject-matter of claims 1-27 is novel in the sense of Article 33(2) PCT.

Inventive Step:

5.1 D1 is regarded as the closest prior art for the inventive step assessment of the subject-matter of claims 1-27 and discloses the compound 5H-imidazo[4,5-c]pyridine,5-[[6-(2,4-difluorophenyl)-3-pyridazinyl]methyl]-2-(2-fluorophenyl) used to treat HCV (see D1: example 317 page 189; description page 1).

5.2 The compound of claim 5 differs from the example of D1 in that it possesses trifluoromethyl groups in position 2 and 4 of the phenyl ring attached to pyridazine ring, whereas in the example of D1 the said phenyl ring is substituted by fluor atoms at the said positions.

5.3 The problem to be solved can be regarded as the provision of further compounds to be use to treat HCV.

5.4 The solution proposed by the present application is regarded as involving an inventive step in the sense of Article 33(3) PCT because an anti-HCV replicon activity comparative test provided page 43 in the description shows that the compound of claim 5 is 330 more potent than the cited compound of D1. Thus, the compound of claim 5, its process of preparation and the intermediates used in the said process are inventive.

5.5 Thus, an inventive step can be acknowledged for the subject-matter of claims 1-27.

Industrial Applicability:

6.1 Claims 1-15,22-27 relate to a subject-matter which is considered to have an industrial applicability, and therefore the subject-matter of said claims meets the criteria of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

7.1 The relative term "about" used in claims 20-21 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(22) International Filing Date:
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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/638,215 21 December 2004 (21.12.2004) US

(71) Applicant *(for all designated States except US)*: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

(72) Inventors; and
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(74) Agents: **KUTZENCO, Allan, N.** et al.; GILEAD SCIENCES, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
10 August 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZO[4,5-C]PYRIDINE COMPOUND AND METHOD OF ANTIVIRAL TREATMENT

(57) Abstract: The compound 5-((3-(2, 4-trifluoromethyphenyl)isoxazol-5-yl)methyl)-2-(25 fluorophenyl)-5H-imidazo[4,5-c]pyridine, together with the salts and solvates thereof. Also provided are compositions comprising this compound and pharmaceutically acceptable carriers, as well as the use of such compositions in the treatment or prophylaxis of viral infections.

WO 2006/069193 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/046477

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15) the whole document	1-5
P,X	WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005 (2005-07-14) abstract; example 6	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another *citation or other special reason* (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" *later document published after the international filing date* or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2006	13/06/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stroeter, T

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/046477

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3 and 4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/046477

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004005286 A	15-01-2004	AU 2003243846 A1	23-01-2004
		BR 0312547 A	26-04-2005
		CA 2491243 A1	15-01-2004
		CN 1678612 A	05-10-2005
		EP 1521754 A2	13-04-2005
		JP 2005537248 T	08-12-2005
		MX PA04012965 A	16-05-2005
		US 2005239821 A1	27-10-2005
WO 2005063744 A	14-07-2005	NONE	